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POLIOMYELITIS

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CONTRIBUTORS

Robert DEBRÉ — Darline DUNCAN — John F. ENDERS
Matthieu-Jean FREYCHE — Sven GARD — James GEAR — W McD. HAMMON
Hilary KOPROWSKI — H C A LASSEN — Johannes NIELSEN — John R. PAUL
A. M-M PAYNE — A. J RHODES — W. Ritchie RUSSELL
A B SABIN — Stéphane THIEFFRY — W. WOOD



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EPIDEMIOLOGY

EPIDEMIOLOGY OF POLIOMYELITIS

JOHN R PAUL, M.D.

Professor of Preventive Medicine, Yale University School of Medicine, New Haven, Conn., USA

The epidemiological behaviour of poliomyelitis cannot be summarized in simple, didactic, or general statements Ideas and explanations about it have been constantly revised and probably will continue to undergo revision Our present exposition of this subject should be considered in this light.

HISTORY

Acute paralysis in infants, as a disease entity, does not seem to have attracted the attention of physicians before the late 18th century, but apparently by the early 19th century poliomyelitis was widespread geographically, for the earliest clinical descriptions of it came from several areas England, 1795, Italy, 1813, and India, 1823 The disease was regarded at the time as ubiquitous, and due to "teething", "foul bowels", or a "fever". There was no mention, however, of anything suggesting contagion, nor was the condition regarded as a medical problem of any magnitude Furthermore, there are no accounts of large epidemics before 1865 As to how common or how prevalent poliomyelitis was during the greater part of the 19th century, this is a matter for speculation, but Heine [19] of Cannstadt, Germany, was able to collect, in 1840, a considerable series of late paralytic cases; and coincidentally North American "orthopaedic surgeons" of the 1830's made occasional mention, without comment as to rarity, of cases of club-foot due to paralysis, acquired in infancy as a result of teething or fever Apparently, then, the general mid-19th-century situation with regard to infantile paralysis was, in part at least, similar to that found today in certain tropical countries and urban populations, where substandard sanitary conditions exist, where the disease is endemic and limited to infants, and where it is not regarded as a problem of major importance.

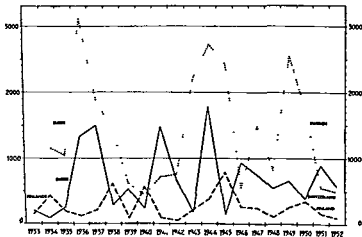
The first indication of anything which might be called an epidemic appears in a report by Sir Charles Bell,[6] the anatomist, in 1836 He stated that a group of cases of paralysis in children had occurred in a relatively

isolated community—namely, on the island of St. Helena. Dr Bell believed that the situation "deserved looking into" In the same year, Badham in England reported four cases of acute paralysis which had occurred more or less simultaneously in the small community of Worksop[5] He also regarded this situation as ominous A few years later a brief report from Louisiana, USA, mentioned a group of eight or ten cases of paralysis, all of them in infants under two years of age[13] But in spite of these limited and scattered outbreaks in the mid-19th century, poliomyelitis was not destined to become quickly recognized as a disease entity with infectious or epidemic potentialities It was not until 1868, when 14 cases were reported in Norway, and later in the 1880's, when Cordier[13a] described outbreaks in France and Medin[31] and others in Sweden, that the epidemic character of poliomyelitis began to be taken seriously Indeed, recognition of this new trend, if so it can be called, was for some 25 years limited largely to northern Europe, and it was another decade before Wickman[61] in Sweden (whose classic work was done before the discovery of poliomyelitis virus) laid the basis for the modern epidemiological concept of this disease, with emphasis on its infectious nature, its spread through human contact, and the importance of mild cases and carriers Since 1900, however, and with ever-increasing rapidity, epidemics of this disease appeared in Europe, North America, and elsewhere From a comparative curiosity, infantile paralysis became a periodic scourge

Once the pattern of epidemicity had been started, it has apparently been irreversible Areas and approximate dates when this transition began are Norway, 1868, Sweden, 1880, parts of western Europe in the 1880's or 1890's, the northeastern section of the USA in the 1890's; the south-eastern section of the USA about 1910, etc Still more recently, i e, within the past 20 years, has this epidemic evolution of the disease come to pass in tropical and semi-tropical areas, such as Puerto Rico, Hawaii, Malta, Salvador, and the island of Mauritius In keeping with the idea that poliomyelitis has not usually been considered to be a disease of the tropics, it was usually thought, when these tropical epidemics appeared, that a new disease, or at least a new strain of virus, had suddenly been introduced into the community This may well have been the case in some places, but, on the other hand, many countries had not been aware of the previous endemic character of their cases of poliomyelitis In certain places the native disease only came to the surface when groups of foreigners, such as soldiers, entered the country as "susceptible immigrants", and there these military units acquired poliomyelitis at far higher rates than would have been expected for that age-group in their homelands This was noted in the Philippine Islands as early as 1936,[21] and again during the second World War, not only there,[53] but in Cairo, Egypt;[9, 42] in India;[29] and in China and Korea[41]

IG 1. POLIOMYELITIS CASES REPORTED IN VARIOUS COUNTRIES, 1933-52

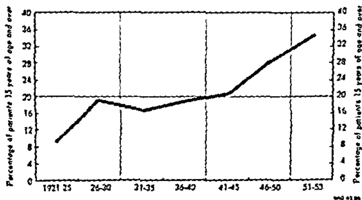
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Once epidemics of poliomyelitis have begun to appear among the local inhabitants of a given region, a gradual or sharp increase in the annual number of cases (as measured over 10-year periods) has usually taken place, and this has steadily progressed. In some countries the annual number of cases has continued to rise over the past 20 years, as in the USA, Canada, and France. In others the number of cases has maintained itself at fairly high levels during this period with widely irregular swings (see fig. 1).

Another type of evolution, which followed the advent of epidemics, has been a gradual shift in age-incidence. During the "pre-epidemic era", poliomyelitis seems to have been almost entirely a disease of infants under five years of age. Indeed, one might term the primitive form of poliomyelitis the true "infantile paralysis". This concentration of 90% of the paralytic cases within the infantile age-group is seldom seen in northern Europe today, for, whereas 40 or 50 years ago maximum attack-rates were nearly always recorded in the 0-4 age-group, it was later found that these had shifted to the 5-9 age-group, or, as in Sweden at present,[35] to the age-groups 7-15, or even 15-25. Although it had long been appreciated that the age-incidence of poliomyelitis will vary with the concentration of population—i.e., the more densely populated the community, the younger the age of those affected—it was not until about 1930 that it became evident that this trend of a general increase in the age of patients was becoming almost worldwide. Burnet[7] was a pioneer in placing emphasis on the epidemiological significance of this trend. Today, in the north-eastern part of the USA, as many as 35% of the patients may be 15 years of age or older[45, 50] (see fig. 2), and in Sweden the percentage is still larger. As adult cases are apt to be more severe, with the rising age-incidence the cases are more readily diagnosed, and the attack-rates increase accordingly.

FIG. 2. THE RISING AGE OF POLIOMYELITIS PATIENTS IN CONNECTICUT, USA, 1921-53



For these reasons alone it is easy to see how the epidemic form of poliomyelitis has attracted much more attention, more alarm, and more study than has the endemic disease

Most of this article will be concerned with a review of evidence as to what has been responsible for this historical evolution of poliomyelitis. It will also be concerned with newer measurements on which these explanations are based, which have now made it possible to estimate the immunity status against poliomyelitis existing within certain populations and communities

GEOGRAPHICAL DISTRIBUTION

Since 1900 it has become apparent that poliomyelitis is a disease which is practically worldwide in distribution, and there is no reason to believe that the disease will not penetrate to any part of the inhabited globe However, the epidemiological behaviour and, pari passu, the clinical behaviour of poliomyelitis, vary greatly in different places, from that of extreme endemicity, as a disease confined to infants, to that of recurrent epidemics with involvement of the older age-groups The endemic form is common in certain tropical areas, particularly in cities where sanitary arrangements are substandard It has even been said that poliomyelitis is actually a tropical disease which strays periodically into the northern or southern temperate zones This is probably an over-simplification of a complex situation, and is certainly one of the epidemiological problems which is in urgent need of further study

MODES OF SPREAD

Human Contact

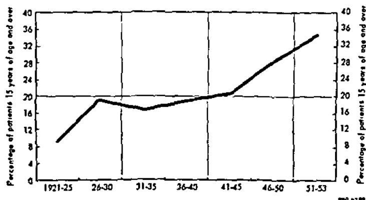
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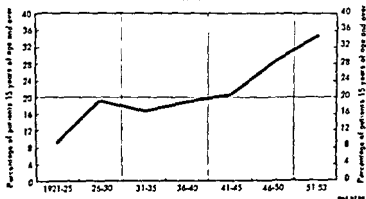
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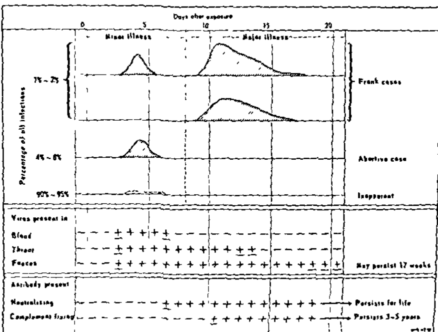
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certain diagnostic terms, referring to severe and mild forms s, and to inapparent infections, requires some definition point They can be illustrated schematically by diagrams which appear in fig 3, and are shown because the relative frequency of each form is of some epidemiological importance

FIG. 3 SCHEMATIC DIAGRAMS OF THE CLINICAL AND SUBCLINICAL FORMS OF POLIOMYELITIS, SHOWING PRESENCE OF VIRUS AND ANTIBODIES IN RELATION TO THE DEVELOPMENT AND SUBSIDENCE OF THE INFECTION



Shaded areas denote periods of fever

Descriptive terms which have been commonly used to designate these various forms are as follows *Paralytic poliomyelitis* is an example of the *major illness* in which weakness or paralysis of one or more muscles develops *Non-paralytic poliomyelitis* is also an example of the *major illness* of poliomyelitis, with involvement of the central nervous system (CNS), as manifested by spinal-fluid changes or appropriate clinical signs, but in which acute or residual paralysis does not occur. *Abortive poliomyelitis* is a brief systemic illness, often limited to one or more of the following symptoms (which are the same as those of the *minor illness*): sore throat, headache, vomiting, and fever; and in which clinical or laboratory signs pointing to CNS involvement fail to develop. Obviously, therefore, abortive poliomyelitis can be diagnosed only in epidemic times *Inapparent*

infection, which is much the most common, occurs in those individuals who sustain silent infection, and who, as a result of this experience, develop antibodies to the infecting strain

Although any one of these forms of poliomyelitis may be responsible for the spread of the disease, there is evidence to suggest that paralytic cases excrete particularly large quantities of virus.[60] Healthy carriers, on the other hand, are by far the most numerous and uncontrolled, as their symptom-free infection escapes detection not only by the clinician but by the health officer Theoretically, then, such cases can act as a huge human reservoir for the spread of the disease and perhaps for the maintenance of the virus in a community during inter-epidemic periods

There have been various attempts since the time of Caverly in 1894,[10] and Wickman in 1905-6,[61] to measure the ratio of mild (and inapparent) poliomyelitis infections to paralytic cases Granted that these ratios will differ within different age-groups and under other circumstances, if the clinical cases only are included one may find ratios of frank (paralytic and non-paralytic) cases to minor illnesses (usually abortive poliomyelitis) which range from 1 5 2 to 1 7.5[45] (see table I) As to the ratio of paralytic to inapparent infections, these measurements are more difficult Indirect estimates by Melnick,[32] based on the finding of poliomyelitis virus in the sewage emanating from a New York City drainage-area serving 625,000 people at a time when only four local cases had been reported, yielded a ratio of clinical to silent infections of about 1 1,000. Previously, Collins[12] had estimated a ratio of 1 100 from historical data on poliomyelitis in large groups of people in the USA Another estimate[24] has been 1 200 Recently, however, new serological methods of determining poliomyelitis antibodies have put us in a far better position to measure this ratio more exactly In Melnick & Ledinko's studies[34] of an epidemic in North Carolina, USA, the age-specific inapparent-infection-rates, as

TABLE I OBSERVED AND MEASURED RATIOS OF FRANK AND PARALYTIC CASES TO MILD AND INAPPARENT POLIOMYELITIS INFECTIONS RESPECTIVELY

Age-groups (years)	Ratios of	
	frank cases (major illness) to abortive cases *	paralytic cases to inapparent infections **
0-1	0	1 175
1-4	1 5 2	1 86
5-9	1 7 7	1 62
10-14	1 7 5	1 95

* Data from community surveys in Connecticut and Pennsylvania, USA, in 1931 and 1932[45]
** Data from North Carolina, USA, in 1948[34]

determined serologically for type 1 virus, were compared with the age-specific clinical (paralytic) attack-rates These ratios according to various age-groups also appear in table I.

It is clear that if the mild (abortive) cases and the inapparent infections are included in any epidemiological survey, then poliomyelitis attack-rates approach those of a highly contagious disease, giving quite a different concept from that gained from analyses of the paralytic cases alone

Another example of the ready communicability of poliomyelitis is the speed of spread with which an epidemic travels peripherally from a central focus through susceptible populations or communities. In semi-rural or rural communities, the peripherally-spreading waves have been variously estimated to move at a rate of 0 1-0.5 mile (about 0 16-0 8 km) per day [8, 40] Obviously this depends in part on local methods of transportation. One particular observation of this type occurring in 1951 among relatively isolated islands in French Oceania is worth recording.[22, 56]

In December 1950 an epidemic of measles began on the island of Tahiti and quickly assumed mammoth proportions, spreading to all the islands of the Society groups—Tuamotu, Austral, and the more distant Marquesas group—within a period of from two to three months It was the first appearance of measles in these islands for 22 years, and about 90% of cases occurred in individuals who were less than 22 years of age Shortly afterwards, in March 1951, an epidemic of poliomyelitis also began, and scattered cases of poliomyelitis soon appeared on all these same islands, including the Marquesas group and spreading at about the same rate as the measles epidemic (or faster) The similarity of the pattern of spread from island to island of these two contact-diseases is striking

Pathogenesis

Portals of entry

How the virus of poliomyelitis actually enters or leaves the human body, how man becomes infected, and how he can contaminate his immediate environment, are matters deserving much further attention and study Shortly after the discovery of the virus by Landsteiner & Popper in 1908,[27] Kling et al.[26] in Sweden set out to determine how frequently poliomyelitis virus might be isolated from the throat, and from the faeces of clinical cases, and laid the groundwork for many further clinical and virological investigations of the epidemiology of poliomyelitis In support of the idea that poliomyelitis is a disease of the alimentary tract were early experiments by Kling et al ,[25a, b] which helped to lay the groundwork for current theories which now favour the mouth as the usual portal of entry.

Earlier arguments favouring the nose as an important portal of entry were based on the observations that poliomyelitis virus could be detected in the human throat early in the disease and, furthermore, that it had been found easy to infect rhesus monkeys by instilling the virus into their nostrils. However, the significance of this ability to infect rhesus monkeys intranasally began to lose some of its force when it became apparent that an increasing number of other neurotropic viruses were also infective if instilled into the nares of experimental animals For instance, this can be accomplished with yellow-fever virus in mice, and occasionally with rabies virus, although it is obvious that such laboratory manoeuvres do not tell us much about the manner in which yellow fever or rabies infects man Next, it should be pointed out that seasonally poliomyelitis does not seem to be a "respiratory disease". Finally, Sabin & Olitsky[53] discovered that lesions may be regularly produced in the olfactory bulbs of the monkey when infection with poliomyelitis virus is induced via the intranasal route Such olfactory lesions were not produced when infection resulted from other routes of inoculation Thus the rarity of olfactory-bulb lesions in fatal cases of human poliomyelitis becomes a significant finding

The alimentary tract—and this includes the mouth, stomach, and entire intestinal tract—seems much more likely as a portal of entry from an analysis of the clinical circumstances under which infection occurs Further evidence supporting this interpretation rests on work with experimental animals in that there are certain species of monkeys, notably the Java monkey (*Macaca cynomolgus*), and the higher apes, such as chimpanzees (*Pan satyrus*), which can be readily infected by being fed the virus In the apes, as in man, most of the infections induced via this route are inapparent

The cutaneous route of infection has never received particular attention but cannot be disregarded, for conceivably it could be a significant portal in the human disease At least with some strains of the virus cutaneous infection can be readily demonstrated experimentally in various species of monkey

Our knowledge of portals of entry in man can therefore be summarized with the statement that it now seems unlikely that the nasal mucosa or the olfactory bulbs represent the usual or the most important human portal of entry in poliomyelitis The oral cavity and the alimentary tract seem more likely, the cutaneous route is a possibility

Distribution of virus within the body

Although virus may be widespread in the body early in the clinical disease, it has certain sites of predilection, such as the pharynx, lymphoid tissue, intestine, and CNS Only in the CNS does it produce serious

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by pharyngeal (or faecal) material may be involved Families may form a focus with a high density of infection, and a number of studies indicate that there is a much lower incidence of infection among extra-household associates than among intra-household groups; and a still lower incidence among non-contacts exists in the same neighbourhood[15]

Environmental Factors in Spread

Important as the direct-contact explanation for the spread of poliomyelitis is, it is not the whole answer, for although seasonal trends occur in a number of diseases spread by human contact, no satisfactory reason has as yet been proposed to explain why the effect of season in poliomyelitis is so sharp and dramatic, and why epidemics of poliomyelitis occur at such a higher rate in the summer and early autumn than in the winter There are several possible explanations · something happens during summer weather which either introduces virus into a community, or enormously facilitates the dissemination of virus throughout a community, or makes certain people, the non-immune, far more susceptible. In any event it does seem that man can contaminate not only his fellow associates, but his immediate environment, and it is possible that an analogy can be drawn in this respect between poliomyelitis and salmonellosis

As an example of contamination of the environment, poliomyelitis virus has been found not only in human faeces, but under natural circum-

[illegible]

periods of the year does not necessarily mean that this is the usual avenue of infection. It means, essentially, that here is evidence that the community is infected, without assuming that the infection is being spread by sewage Tubercle bacilli can, for instance, be found with great frequency in urban sewage, yet one does not usually regard sewage as the source of spread of tuberculosis through a community Seldom has there been evidence to incriminate the water-supply as a source of poliomyelitis infections, although several observers have laid emphasis on the possibility of this occurring, notably Dr Kling and his co-workers in Sweden.[25] In only a few outbreaks have there been reasons to consider that milk had been contaminated with the virus and was the source of the infection

Insects

As to insects, a variety of arthropods have been suspected from time to time of spreading poliomyelitis Many varieties have been tested for the presence of virus Such tests have yielded no positive results except

lesions. In man, very early in the disease, or late in the incubation period, the virus has been recovered from the blood-stream. The same is true of chimpanzees and cynomolgus monkeys after being fed the virus However, such points as the extent to which this demonstrable viraemia indicates the route along which the virus travels on its way through the blood-brain-barrier and into the CNS, and whether it is merely what might be called a passive spill-over from various early sites of localization within the body, such as lymph-nodes, have not been settled.

As to portals of exit, during and after an acute attack of poliomyelitis the virus can be demonstrated in the oropharynx for about a week from onset, whereas it exists in the intestinal tract from three to six weeks or even longer. Again it should be emphasized here that this acute and convalescent carrier-state can often be initiated by an attack so mild as to go unnoticed Faeces, therefore, provide a rich and persistent source of virus As much as one million infectious doses for the monkey have been detected in a gram of faeces. If opportunities for the direct transfer of faecal contamination to the mouth are frequent, it is understandable how infection with poliomyelitis virus could be easily acquired. Just what the virus of poliomyelitis is doing in the intestinal tract and how it is maintained there are questions as yet unanswered, but, epidemiologically speaking, it seems to be a dangerous place to find a highly infectious virus.

Infectiousness of people

Before leaving the question of the pathogenesis and spread of poliomyelitis virus, attention should be called to the fact that, as in other virus diseases such as measles, the early days of illness seem to be much more infectious than later This may be a matter of dosage of virus. In poliomyelitis it could, in part, be due to the fact that in the first week of illness and before (during the prodromal or viraemic period) (see fig. 3, page 14) virus is exuding or being excreted from both the pharynx and the intestinal tract of the patient in large quantities Later its presence is limited to the intestines, from which virus may continue to be excreted for as long as 17 weeks from onset [28] Long-term human carriers, however, who excrete the virus for years—comparable to persistent carriers in typhoid fever—have not been discovered

As to the type of contact which results in the transfer of infection from one person to another, it is safe to say that poliomyelitis can be acquired by the close association of an infected person with non-immune people. This type of contact can be enhanced by crowding within living quarters or elsewhere. It is easy to see how readily it can occur in the intimate associations between children, and how a young child's infection can be readily transferred to a susceptible mother Contamination of hands and utensils

by pharyngeal (or faecal) material may be involved. Families may form a focus with a high density of infection, and a number of studies indicate that there is a much lower incidence of infection among extra-household associates than among intra-household groups; and a still lower incidence among non-contacts exists in the same neighbourhood [15]

Environmental Factors in Spread

Important as the direct-contact explanation for the spread of poliomyelitis is, it is not the whole answer, for although seasonal trends occur in a number of diseases spread by human contact, no satisfactory reason has as yet been proposed to explain why the effect of season in poliomyelitis is so sharp and dramatic, and why epidemics of poliomyelitis occur at such a higher rate in the summer and early autumn than in the winter There are several possible explanations: something happens during summer weather which either introduces virus into a community, or enormously facilitates the dissemination of virus throughout a community, or makes certain people, the non-immune, far more susceptible. In any event it does seem that man can contaminate not only his fellow associates, but his immediate environment, and it is possible that an analogy can be drawn in this respect between poliomyelitis and salmonellosis

As an example of contamination of the environment, poliomyelitis virus has been found not only in human faeces, but under natural circumstances in urban sewage, [17, 46, 49] and in faecal material collected in open privies [16] As to the significance of this, emphasis should be placed on the fact that the mere presence of poliomyelitis virus in sewage at certain periods of the year does not necessarily mean that this is the usual avenue of infection It means, essentially, that here is evidence that the community is infected, without assuming that the infection is being spread by sewage Tubercle bacilli can, for instance, be found with great frequency in urban sewage, yet one does not usually regard sewage as the source of spread of tuberculosis through a community Seldom has there been evidence to incriminate the water-supply as a source of poliomyelitis infections, although several observers have laid emphasis on the possibility of this occurring, notably Dr Kling and his co-workers in Sweden [25] In only a few outbreaks have there been reasons to consider that milk had been contaminated with the virus and was the source of the infection

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southern temperate climates the disease is more prevalent, in both its epidemic and non-epidemic forms, in summer than in winter. This refers not only to overt, clinical cases, but also to inapparent infections. A demonstration of the periodic contamination of the environment by inapparent infections appears in the results of a series of tests on monthly samples of the sewage of New York City over a period of six years,[32] and in Toronto, Canada, over a period of 12 months.[49] In both urban communities poliomyelitis virus could be isolated fairly regularly in the late summer and autumn of the year but not during the rest of the year Turner's serological studies in Baltimore, USA,[58] covering a period of about five years, also revealed that antibodies to type 2 poliomyelitis virus were acquired by children almost entirely during the summertime, and again almost entirely as the result of asymptomatic infections. Certain meteorological conditions apart from temperature, such as rainfall and humidity, have long attracted the attention of investigators, but no consistent correlation with the prevalence of poliomyelitis has been established which would indicate a close relationship with these factors.

Host factors, predisposing to or precipitating paralysis

The possibility that factors other than the biological characteristics of the strain of virus causing the infection may influence the clinical course of this disease, and particularly the development of paralysis, has been recognized for some years Indeed, in the late 19th century, before the discovery of the virus, the view was held that "trauma" might be the only cause of infantile paralysis Today, this idea of trauma, although somewhat modified, is again receiving acceptance, but this time as a "precipitating", not a direct, cause. Thus, experience does indicate that, during an epidemic, injuries ranging from trauma of moderate severity to a fracture can be regarded as having an unfavourable influence on poliomyelitis To this should also be added certain surgical operations, such as tonsillectomy, adenoidectomy, and the extraction of teeth, which may be followed by the appearance of paralysis An important example of this is the increased incidence of bulbar poliomyelitis in persons subjected to tonsillectomy and adenoidectomy within the previous month [1, 4] There also seems to be little doubt that if over-exertion and fatigue are experienced at the time of onset of the major illness, it is particularly liable to be followed by severe paralysis [23, 51] Furthermore, there is recent evidence to indicate that an association exists between intramuscular injections and the subsequent appearance (within a month) of paralysis in the injected limb,[2, 20, 30] so-called localized or segmental paralysis. In particular, the combined diphtheria-pertussis vaccine has been suspected There is no exact explanation as to how this comes about, but it is possibly a matter of timing in this disease, when the effect of fatigue or of trauma

in the case of flies,[54, 57] and, more recently, cockroaches.[55] It is now abundantly clear that various species of flies may carry the virus, particularly the faecal-feeding species,[17] and it is clear, also, that naturally-infected flies can contaminate food with poliomyelitis virus.[59] However, there is no reason to regard insects as an essential or a dominant element in the spread of this disease In some epidemics, which have occurred in the Arctic during winter, it would seem definite that flies could have played no part Campaigns to reduce the number of, or to eliminate, flies have apparently not lessened the incidence of poliomyelitis [38, 39] On the other hand, in certain areas where sanitary conditions are substandard and flies are exceedingly common, it is quite possible that the role which these insects may play as mechanical vectors in spreading the virus of poliomyelitis may be appreciable [17] The word mechanical is used advisedly here, for there is no evidence that poliomyelitis virus multiplies within flies [35]

Whether or not a biting or blood-sucking insect could play any accessory part in the spread of poliomyelitis is a possibility which has been lightly dismissed; perhaps too lightly, because the recent finding that poliomyelitis virus is present in the blood-stream in prodromal periods of the clinical disease reopens this whole subject for future study It may be mentioned, in this connexion, that Japanese investigators described in 1941 the survival of poliomyelitis virus within artificially infected mosquitos (*Culex pipiens*) for periods lasting as long as three weeks.[37]

Environment

To summarize what is known about the survival of poliomyelitis virus in nature and outside man, one can say that environmental factors certainly exist in this disease and could enhance its spread. This is primarily manifested by the fact that infection and immunity are so uniformly acquired by infants in areas and communities where infant mortality is high, and where poor sanitation and much faecal pollution of the environment exists. Conversely, in areas of good sanitation exposure is more diffuse, infection-rates are reduced, and the disease is usually acquired not in infancy, but at a later age In this respect poliomyelitis might be correctly designated a "place disease", granted, of course, that one recognizes that, as such, the influence of environment is that of providing facilities for the spread of poliomyelitis virus from person to person

Climate and season

Poliomyelitis is also a "time disease" for, as already mentioned, climate and season exert a profound although poorly understood effect upon its epidemiological behaviour In tropical areas, cases occur more or less uniformly throughout the year, whereas in both northern and

the opportunity offers Few more graphic examples of this are at hand than that of the poliomyelitis epidemic among Eskimoes in the Canadian Arctic in 1948-9, which has been described by Peart [47] Here the disease was first introduced into settlements along the west side of Hudson Bay and spread rapidly northwards, reaching the remote settlement of Chesterfield Inlet where the epidemic involved almost 60% of the entire population with paralytic disease, attacking all age-groups, the lowest clinical attack-rate being in the infants! This fact reminds us that, as in measles, the age-distribution of cases of poliomyelitis within a community or population can also be taken as an indication of the state of immunity of that population, which in the case of these Eskimoes must have been exceedingly low

Today, however, measurements besides those of age-specific case-rates can actually be made in advance of an epidemic, which may enable the epidemiologist to evaluate the immune status of a given population This has been done in many areas by determining the percentage of those healthy individuals in the chosen population who possess antibodies capable of neutralizing one or more types of poliomyelitis virus. Such antibodies indicate whether the individual who possesses them has ever been infected in either the recent or the distant past, complement-fixing antibodies, on the other hand, indicate recent infection

In two remote Eskimo communities, north Alaska,[44] and Baffin Island,[2] it has been found from serological surveys that, as might have been expected, there was a dearth of neutralizing antibodies of all three types of poliomyelitis virus in a very substantial percentage of the young adult population

In certain tropical areas, both urban and semi-urban, the situation is quite the opposite Using a very crude test, it had been demonstrated as early as 1935 that, surprisingly enough, a very high percentage of normal individuals from tropical locations possessed poliomyelitis antibodies Later, with the introduction of the mouse neutralization test for type 2 (Lansing) poliomyelitis virus, such surveys made in areas with substandard sanitation, many of them in the tropics, showed that almost all healthy children over the age of four or five years possessed type 2 poliomyelitis antibodies, indicating that they had already been infected with this strain and had gained immunity [15, 43] Although the neutralizing antibody tests were only for one type (i e , 2), it appears that this type 2 antibody is a fairly good index of immunity to poliomyelitis in general [43] As an example of this, an examination has been made in two cities—Cairo, Egypt, and Miami, Florida, USA—both of which are located in the same latitude In both, the ages at which type 2 poliomyelitis-neutralizing antibodies were acquired have been compared with the ages at which clinical poliomyelitis was acquired (see fig 4) The percentage of those in each age-group

is sustained *during the period of viraemia*, it tips the balance in an unfavourable direction in persons already infected with poliomyelitis virus, who ordinarily might have developed an inapparent, abortive, or non-paralytic attack

As to other contributing causes, which concern the host rather than the virus, much has been written about the role of genetic constitution and of the fact that a high rate of paralysis has prevailed through several generations in certain families It is well established that pregnant mothers are particularly vulnerable to poliomyelitis This may be an example of the effect of endocrine factors increasing the susceptibility of the patient, possibly related to the manner in which cortisone may increase the susceptibility of experimental animals.[3]

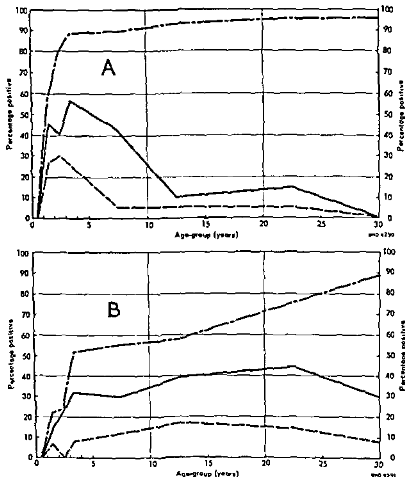
In summary, therefore, with regard to these host factors, although it is impossible to say why, of all those infected with poliomyelitis viruses, only 1 in 100 or fewer may develop paralysis, one can say that there are at least some "traumatic" or other experiences which are known to influence this ratio in an unfavourable direction

SEROLOGICAL-EPIDEMIOLOGICAL STUDIES

Thanks to discoveries by Enders and his co-workers, who have shown that poliomyelitis viruses may be grown in non-nervous tissue cultures,[11] a relatively new and special approach has been opened up for the measurement of poliomyelitis antibodies on a large scale. This approach yields measurements comparable to those found in tuberculin-test or Schick-test surveys In other words, it differentiates the immune from the susceptible persons within a given population It is clear, of course, that immunity and the presence of antibodies are not one and the same thing, and that the significance of various antibodies differs, but there is a general pattern of relationship which allows one to use this approach in poliomyelitis epidemiological surveys when determining the "immune status" of a given population

Poliomyelitis is apparently one of those diseases which, like measles, is "under pressure" to spread into a susceptible population, usually representing the younger age-groups, and it will do so whenever the virus has access during the appropriate season to such a population, unless that pressure is removed by artificial or special circumstances. Today, there are few communities, no matter how small or remote, which can hope to escape periodic contact with this virus for long, and, if the inter-epidemic period is long, the risk of a potentially severe epidemic increases annually, as the population composed of susceptible infants, children, and even young adults, is built up. This susceptible population therefore represents a kind of vacuum of growing size into which the virus may surge when

FIG. 5. COMPARISON OF NEUTRALIZING ANTIBODY PATTERNS WITH COMPLEMENT-FIXING ANTIBODY PATTERNS IN TWO POPULATIONS (A: CAIRO, EGYPT; B: CHARLESTON, W.VA., USA)



The values indicated in this graph correspond to the age-groups < 1, 2, 3-4, 5-9, 10-14, 15-29, and 30+ years

A = Cairo, Egypt B = Charleston, W Va, USA

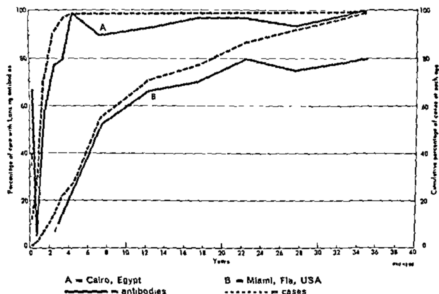
—·—·— = neutralizing 1 : 2 dilution of serum

——— = complement-fixing 1 : 4 dilution of serum

– – – = complement-fixing 1 : 16 dilution of serum

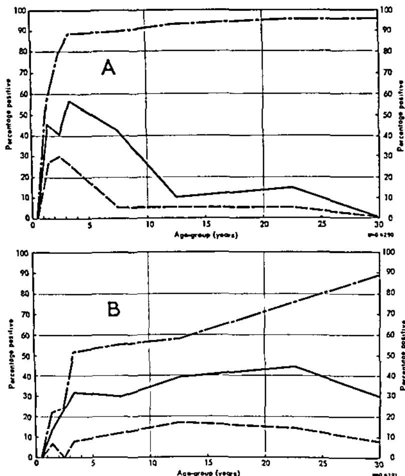
who have had poliomyelitis is shown here, charted on a cumulative basis. Without a proper adjustment of variation in the age-distribution of the two population groups, these curves are not strictly comparable. But generally this case-rate graph runs fairly close to that recording the rates at which type 2 neutralizing antibodies were acquired The speed at which poliomyelitis infections (both apparent and inapparent) were acquired during childhood differs in the two countries. The Miami curves show a delayed rise in contrast to the Cairo curves The latter are similar to curves derived from surveys in North Africa, the West Indies, and certain small towns in southern Texas, USA,[43] whereas the former are similar to those found in many other cities in the USA, and in one European city (Munich, Germany)[43]

FIG. 4. COMPARISON OF TYPE-2 NEUTRALIZING ANTIBODY PATTERN WITH CUMULATIVE ATTACK-RATE OF POLIOMYELITIS IN POPULATIONS FROM TWO SUBTROPICAL AREAS



It has also recently been possible to carry out complement fixation tests on sera from a given population From analyses of neutralizing and complement fixing antibodies in the survey, one can determine what the story has been with regard not only to infections in the past but also to those which have occurred recently, i e , within from three to five years.[33] This is based on the fact that complement fixing antibodies do not remain elevated for longer than three to five years, and perhaps even less.

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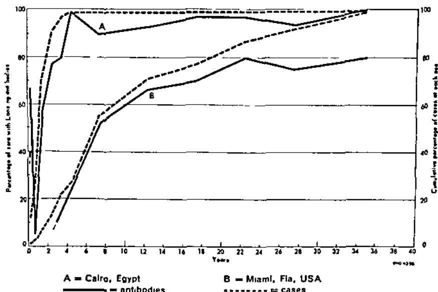
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A number of methods which utilize greatly-improved techniques for the determination of antibodies against poliomyelitis virus have clarified some of the previously existing epidemiological puzzles In its new perspective, the spread of poliomyelitis now appears to occur not only through direct contact between individuals, but through contamination of an infected individual's immediate environment. This is well brought out by the different behaviour of the disease in those urban areas where the sanitary arrangements are deficient In communities where sanitation is primitive and living conditions are crowded and poor, facilities for the spread of such a virus are better than elsewhere, consequently, infants have the opportunity of coming into contact with all three types of poliomyelitis virus early in life, and few of them reach the age of three or four years without having been infected with at least one strain, although clinically the infection, to a very large degree, is inapparent Therefore, immunity is acquired early and silently in such areas, and no large group of susceptibles is built up. Within such communities the disease smoulders, and epidemics of poliomyelitis are not liable to occur [17] In countries where the sanitary arrangements are no longer primitive, the risk of contact with the virus at an early age is diminished. A large percentage of the juvenile population reaches the age of six, eight, or ten years without having acquired any infection or any immunity, and consequently such populations are ripe for epidemics, which sooner or later seem to appear. It would seem questionable whether this situation is desirable In any event, if one is to be concerned with the prevention of poliomyelitis, some means of artificial immunization would seem to offer far more hope than attempts to rid the environment of poliomyelitis virus

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By including both neutralizing and complement-fixation results in surveys from two different cities—Cairo, Egypt, and Charleston, W. Va, USA—(see fig 5) one can compare the two (J L Melnick, unpublished data) In the former population (at the left of the figure) there is evidence of heavy exposure in early life to poliomyelitis virus; young children in Cairo make antibodies up to the age of three or four years. By the age of five or six they have reached immunological maturity as far as this disease is concerned, thus eliminating the threat of adult poliomyelitis. This fact is also borne out by the extreme dearth of adult clinical cases in locally born citizens within this or other areas where the infantile disease has prevailed It is very different from the story in Europe (including Sweden), North America, Canada, and Australia, where, as was emphasized earlier in this article, adult poliomyelitis is so *common*. This is reflected in the delayed rise in neutralizing antibodies in the curve derived from the population in Charleston, W Va (see fig. 5 (B)), which does not reach 90% until the age of 30 The prolonged elevation of the curve measuring complement fixing antibodies also indicates that immunological maturity has been postponed

The above results record findings concerned with only one strain of the virus. With the introduction of tissue-culture methods, it is now possible to carry out neutralization and complement-fixation studies with all three types In general, the results of these triple surveys are the same as those with type 2 virus alone, indicating that in some populations infants are infected two, and sometimes three, times in the early years of life, so that antibodies to one, two, or three types are present in about 80% of the population by the time they have reached five years of age. The corresponding curve for complement fixing antibodies shows a peak at the age of six or seven, followed by a rapid fall, again indicating that the infections are all concentrated in this low age-group (D. M Horstmann & J. R Paul, unpublished data).

CONCLUSIONS

In summary, therefore, it appears that epidemiological thinking in poliomyelitis has undergone a number of revisions in the past generation. From an endemic disease it has become epidemic in many places, and, indeed, has become a common periodic scourge Originally regarded as a disease limited to infants, it is no longer confined to infancy From being considered as mildly contagious or infectious, it is now regarded as highly infectious From being an infection in which the clinical picture was originally thought to be limited to acute paralysis, it is now regarded as one in which one case in a hundred, more or less, of those infected becomes

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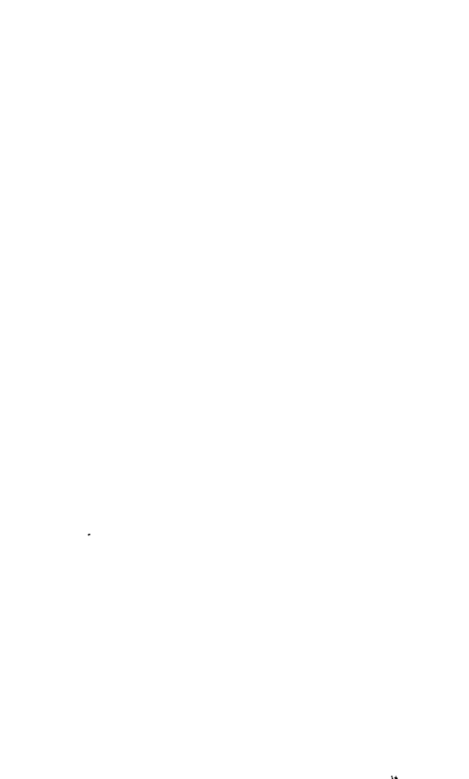
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POLIOMYELITIS IN THE UNDER-DEVELOPED AREAS OF THE WORLD

JAMES H S GEAR, M.B., Ch.B , B Sc ,
D P.H., D T.M. & H., Dip Bact

Director of Research,
Laboratories of the Poliomyelitis Research Foundation,
South African Institute for Medical Research,
Johannesburg, Union of South Africa

One of the most perplexing facts in the history of infective diseases is that the incidence of paralytic poliomyelitis, in contrast with almost all the other infective diseases, is increasing. It is only within the last century that paralytic poliomyelitis has assumed epidemic form The extensive epidemics which have appeared only within the last fifty years occurred first in Scandinavia and in the USA, and then later in Australia and New Zealand, the countries with the highest standards of living and the best hygiene and sanitation in the world. While these countries were severely affected, the under-developed countries continued to enjoy freedom from epidemic poliomyelitis as they had in the past But in the last decade a new trend of development of the disease—the assumption of epidemic form in one country after another which had previously seemed to be almost free from the infection—has become evident. It is likely that this trend will continue until epidemics involve all countries

It is therefore opportune to examine in detail the occurrence of poliomyelitis in the under-developed areas and to note what factors are at play in determining its incidence This review is particularly opportune at the present time, when it is still possible to contrast the disease as it occurs among people living under primitive surroundings with its manifestations in more highly developed communities. It will also be relevant to discuss what developments are to be expected in the future in the pattern of poliomyelitis in various parts of the world.

Background

The under-developed areas include most of the countries of the world and the majority of its peoples Nearly all Africa, a greater part of Asia, and many regions of the Americas, as well as most of the islands in the tropical seas, may be classified as under-developed areas These

vast regions include an infinite variety of topographical and climatic conditions ranging from tropical desert through tropical jungle and rain forest to lands often snow-covered. They include some of the most sparsely inhabited areas, as well as the most densely populated countries The people in these regions differ from one another in ethnic origin, in the food they eat, and in the work they do, and have a great variety of customs and ways of living Nevertheless, the under-developed areas have certain features in common which entitle them to that description. Although communities living under primitive conditions exist within the Arctic Circle, most of the under-developed areas are to be found within the tropics and subtropics.

The indigenous population in many of these countries may, broadly speaking, be divided into two sections: those persons who live as their ancestors did in rural areas, and those who have migrated to the neighbourhood of recently established towns where they often live in slums The housing conditions of most of these people, whether in rural or urban areas, are primitive Often they live in grass or reed huts or in houses made of logs, mud-brick or stone, or corrugated iron. As most of these areas have tropical and equable climates, the lack of well-constructed houses probably has little adverse effect on the health of the people, perhaps the reverse However, in addition to poor housing, there is also often gross overcrowding. Of great importance, too, is the comparative or complete lack of sanitation and of purified water-supplies, indeed, the water is usually heavily polluted

The health of the people in the under-developed areas has recently been the subject of intensive investigation Many of these studies have been sponsored by the World Health Organization and the situation is now so well known that a detailed description is not necessary Only the salient features relevant to the present review will be briefly noted.

Malnutrition and undernutrition of various grades and kinds are the rule Diseases, particularly alimentary infective diseases, are prevalent. Malaria, relapsing fever, and yaws, and many other diseases affecting the masses, are endemic in many regions The people in many parts of these areas also suffer severely from various helminthic infestations, this depends largely on the nature of the country and the distribution of mollusc intermediate hosts The infant mortality-rate is appallingly high, while the expectation of life of those who survive their first year is relatively low.

Geographical Incidence of Poliomyelitis

The known facts about the geographical distribution of poliomyelitis were summarized by Rhodes [21] in 1948. He noted that, until comparatively recently, poliomyelitis has not been generally regarded as a problem

in tropical medicine as it was a rare disease, occurring sporadically and with little epidemic prevalence He also noted that during the past ten years the disease has proved unexpectedly prevalent among British, American, and other Allied troops serving in China, India, Japan, the Middle East, and the Philippine Islands

The occurrence of cases among these troops drew attention to the presence of poliomyelitis virus in communities where the disease did not appear to be prevalent in the native population at the time [22] Paul,[21] in 1949, made a detailed study of the poliomyelitis attack-rates in American troops between 1940 and 1948, and summarized the position thus The rates at which the United States troops contracted poliomyelitis during the period under review were different in different parts of the world, rates in the Far East and in the Philippine Islands being higher than elsewhere. One likely explanation is that a large amount of poliomyelitis virus exists and persists in areas throughout the world where previously it has been the custom to consider poliomyelitis as rare Paul also noted that clinical poliomyelitis may be much more prevalent in some areas, including tropical and semitropical areas, than has previously been realized

Sabin,[26] in a review of the epidemiological patterns of poliomyelitis throughout the world, noted that the risk of acquiring paralysis as a result of infection with poliomyelitis virus is not the same for all population groups in the same region or country and varies markedly for people living in different parts of the world In the greatly overcrowded and unhygienic communities of China, India, the Philippine Islands, and many other parts of the world, paralytic poliomyelitis is still relatively rare, sporadic rather than epidemic, and infantile when it does occur in the native population The recent increased migration of adult Americans and British to these areas has produced not only examples of continued adult susceptibility to paralytic poliomyelitis, but also evidence that the virus was present in abundance in these regions despite the rarity of the paralytic disease among native children Sabin also noted that the incidence of the disease differs in various racial groups in some places but not in others, and that this phenomenon cannot be accounted for by economic status After analysing the data, he concluded that hypotheses based on the concept of latent immunization and possible interplay of many different types of poliomyelitis virus, varying in antigenic complexity as well as in virulence, do not provide satisfactory explanations for the peculiar age-selection.

Olin,[19] after a study of the epidemiological pattern of poliomyelitis in Sweden, stated that the deviation of the age selection of poliomyelitis towards higher age-groups which has been manifested during the past decade in Sweden, as in various other countries, suggests that in the more advanced countries the successive improvement of general hygiene has limited more and more the possibilities of faecal infection The risk of

vast regions include an infinite variety of topographical and climatic conditions ranging from tropical desert through tropical jungle and rain forest to lands often snow-covered. They include some of the most sparsely inhabited areas, as well as the most densely populated countries. The people in these regions differ from one another in ethnic origin, in the food they eat, and in the work they do, and have a great variety of customs and ways of living. Nevertheless, the under-developed areas have certain features in common which entitle them to that description. Although communities living under primitive conditions exist within the Arctic Circle, most of the under-developed areas are to be found within the tropics and subtropics.

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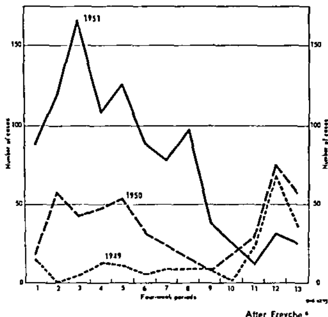
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FIG. 1. RECENT EVOLUTION OF POLIOMYELITIS IN ANGOLA



After Freyche[a]

In French Equatorial Africa, the total number of annual notifications from 1947 to 1950 never exceeded 10 In 1951, 141 cases with 4 deaths were registered. This outbreak was most severe in the areas adjoining the Belgian Congo.

The relatively large epidemic in Angola was also probably related to the outbreak in the Belgian Congo While the annual notifications from 1927 to 1950 never exceeded 34, in 1951, 773 cases with 60 deaths were recorded In the following year there was a considerable improvement, but in 1953 the disease again appeared in epidemic form.

Sharp outbreaks have also been reported recently in Kenya, Northern and Southern Rhodesia, Nyasaland, and Uganda. Although there has been no widespread epidemic since 1948, poliomyelitis continues to occur at a relatively high rate in the Union of South Africa

Table I gives the figures for the occurrence of poliomyelitis during recent years in Africa It is clear from these figures that the disease is endemic in all the countries of Africa Freyche concludes that the idea that poliomyelitis occurs only sporadically must be revised Veritable epidemics may occur in these regions at any time of the year.

coming into contact with the virus at an early age has diminished, which may explain the fall in morbidity at this age When sooner or later the time arrives for first contact with the virus, the probability of a manifestation accompanied by paralysis has grown, for the frequency of paralytic poliomyelitis depends to a large extent on the age at which the growing generation comes into contact with the virus. Should this contact take place in infancy, morbidity will be highest at an early age, while the total frequency will remain low, while if the first infection occurs later in life, the total frequency will be high and the age-specific attack-rate will deviate towards higher age-groups

Gear[11] expressed a similar conclusion. He noted that modern hygiene and sanitation and good standards of living greatly diminish the chances of an infant's being infected with the virus of poliomyelitis. As a result of the lack of early immunizing infections, advanced communities are liable to epidemics. On the other hand, in primitive communities, where the infection is endemic and where circumstances, such as the prevalence of flies and the pollution of water, favour its wide spread, most infants are infected early in life Such communities are not liable to epidemics of poliomyelitis

Recent Outbreaks in Under-Developed Areas

Since these comprehensive surveys were made, there has been ample confirmation that the problem of poliomyelitis is becoming more serious in most countries. In many poliomyelitis may now be regarded as the most important infective disease Freyche[6, 7] has analysed in some detail recent outbreaks in various parts of the world and it will be of value to note his findings

Africa

Geographical incidence

In Africa, within the last five years (1949-54) large epidemics have occurred in Angola (see fig 1), the Belgian Congo (see fig. 2), and French Equatorial Africa

In the Belgian Congo, the recrudescence of the disease, noted in November *1950 in the province of Leopoldville, continued with less important* foci in the provinces of Costermansville, Elisabethville, and Stanleyville during a considerable part of 1951 · 1,009 cases with 41 deaths were registered, of these, 773 (21 deaths) were in the province of Leopoldville and 142 (9 deaths) in the province of Costermansville. In Ruanda Urundi, 53 cases (2 deaths) were notified This outbreak continued in 1952 with but slight abatement, 723 cases (46 deaths) being notified

Racial incidence

In those countries where only relatively small numbers of Europeans have settled, the majority of cases has been in Africans In those countries with a relatively large European population, such as Southern and Northern Rhodesia, it has been noted that the majority of reported cases occurred in Europeans In Nyasaland and Southern Rhodesia there was a disturbing number of paralytic cases, associated with a high death-rate, among adult European settlers of recent arrival Indeed, paralytic poliomyelitis is now one of the most serious disease hazards faced by Europeans in these areas

In the widespread epidemics which occurred in the Union of South Africa in 1945 and 1948, it was possible to compare the incidence of paralytic infections among the indigenous African Bantu population with the incidence among persons of European descent Paralytic poliomyelitis was ten times as frequent in the European as in the Bantu It was also apparent that, among the Bantu population, the majority of cases occurred *in infants under five years of age Among the European population there* were as many cases in the 6-10 age-group as in the 0-5 age-group However, there was no doubt that when the disease was epidemic among the Europeans it was also epidemic among the Africans (see figs. 3 and 4), and that among the latter there was a higher prevalence of paralytic cases than had ever been observed before.

Seasonal incidence

The seasonal incidence of several important recent outbreaks in Africa has been analysed by Freyche,[6] his findings are summarized in table II.

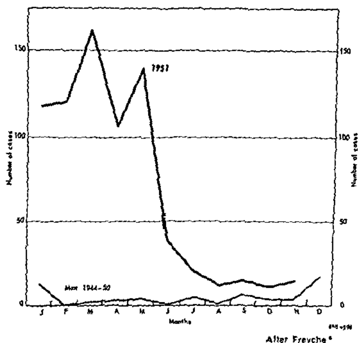
Freyche concludes from this table that poliomyelitis epidemics, doubtless more frequent in the tropical region than generally recognized, may occur at any time of the year There is, however, some tendency for the

TABLE II SEASONAL INCIDENCE OF POLIOMYELITIS IN RECENT EPIDEMICS IN AFRICA

Country	Years	Period of high incidence	Peak
Angola	1951	I – V	III
Belgian Congo	1949–50	XI 1949 – VI 1950	13 XI – 10 XII
	1950–1	XI 1950 – VIII 1951	4 II – 10 III
Mauritius	1945	4 III – 28 IV	4–31 III
	1948–9	5 XII 1948 – 5 II 1949	26 XII – 5 I
Northern Rhodesia	1946	24 II – 18 V	24 II – 2 III
Southern Rhodesia	1951	X – XII	XI
St Helena	1945–6	XII 1945 – I 1946	XII
Union of South Africa	1948	I – VII	28 III

After Freyche[6]

FIG. 2. RECENT EVOLUTION OF POLIOMYELITIS IN THE BELGIAN CONGO



After Freyche[a]

TABLE 1. RECENT INCIDENCE OF POLIOMYELITIS IN AFRICA

Country	1945-51 median	Cases *		
		1950	1951	1952
Angola	15	9	773 (60)	37 (3)
Basutoland		5	3	2
Bechuanaland		0	4	2
Belgian Congo	91	524 (28)	1,009 (41)	723 (46)
French Equatorial Africa	—	5	141 (4)	63 (1)
French West Africa	—	9	25	11
Kenya	60	107 (7)	62 (5)	122 (10)
Northern Rhodesia	11	7 (1)	22 (2)	23 (2)
Nyasaland	8	33	7	
Southern Rhodesia	22	57 (13)	167 (14)	98 (13)
Uganda	—	18 (7)	48 (1)	219 (10)
Union of South Africa	189	189	469	272

* The number of deaths is given in parentheses.

Racial incidence

In those countries where only relatively small numbers of Europeans have settled, the majority of cases has been in Africans In those countries with a relatively large European population, such as Southern and Northern Rhodesia, it has been noted that the majority of reported cases occurred in Europeans In Nyasaland and Southern Rhodesia there was a disturbing number of paralytic cases, associated with a high death-rate, among adult European settlers of recent arrival. Indeed, paralytic poliomyelitis is now one of the most serious disease hazards faced by Europeans in these areas

In the widespread epidemics which occurred in the Union of South Africa in 1945 and 1948, it was possible to compare the incidence of paralytic infections among the indigenous African Bantu population with the incidence among persons of European descent Paralytic poliomyelitis was ten times as frequent in the European as in the Bantu It was also apparent that, among the Bantu population, the majority of cases occurred in infants under five years of age Among the European population there were as many cases in the 6-10 age-group as in the 0-5 age-group However, there was no doubt that when the disease was epidemic among the Europeans it was also epidemic among the Africans (see figs 3 and 4), and that among the latter there was a higher prevalence of paralytic cases than had ever been observed before

Seasonal incidence

The seasonal incidence of several important recent outbreaks in Africa has been analysed by Freyche,[6] his findings are summarized in table II

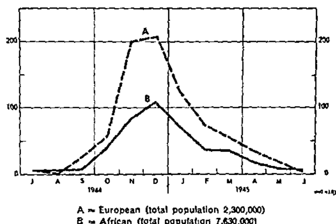
Freyche concludes from this table that poliomyelitis epidemics, doubtless more frequent in the tropical region than generally recognized, may occur at any time of the year There is, however, some tendency for the

TABLE II SEASONAL INCIDENCE OF POLIOMYELITIS IN RECENT EPIDEMICS IN AFRICA

Country	Years	Period of high incidence	Peak
Angola	1951	I – V	III
Belgian Congo	1949–50	XI 1949 – VI 1950	13 XI – 10 XII
	1950–1	XI 1950 – VIII 1951	4 II – 10 III
Mauritius	1945	4 III – 28 IV	4–31 III
	1948–9	5 XII 1948 – 5 II 1949	26 XII – 5 I
Northern Rhodesia	1946	24 II – 18 V	24 II – 2 III
Southern Rhodesia	1951	X – XII	XI
St Helena	1945–6	XII 1945 – I 1946	XII
Union of South Africa	1948	I – VII	28 III

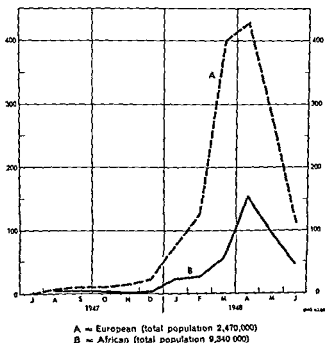
After Freyche[6]

FIG. 3. RACIAL AND SEASONAL INCIDENCE OF POLIOMYELITIS IN THE UNION OF SOUTH AFRICA, 1944-5



A = European (total population 2,300,000)
B = African (total population 7,630,000)

FIG. 4. RACIAL AND SEASONAL INCIDENCE OF POLIOMYELITIS IN THE UNION OF SOUTH AFRICA, 1947-8



A = European (total population 2,470,000)
B = African (total population 9,340 000)

peak of most of the epidemics to occur either in November-December or in February-March—the periods associated, respectively, with the two rainy seasons

Gear,[9] in a study of the seasonal incidence of poliomyelitis in southern Africa, noted that all the epidemics have occurred during the summer and autumn. In the 1944-5 epidemic in South Africa the greatest incidence was in mid-summer In tropical Durban the peak occurred in October, whereas in Johannesburg, which has a temperate climate, the greatest number of cases occurred in mid-December. In tropical Northern Rhodesia one outbreak occurred during September and October, the hot, dry months before the rains Another outbreak occurred in February and March in the midst of the rainy season The 1948 epidemic in Johannesburg did not attain its peak until the middle of March and maintained this high incidence of cases throughout April. On comparing these two epidemics, it is apparent that the temperature was not the deciding factor in determining the time of onset. However, it may be noted that good rains fell early in 1944 and there was an early ripening of fruit and vegetables. In the 1947-8 season the rains were late, and because of the early drought the summer growth of vegetation was delayed. After the rains came the vegetation grew luxuriantly and there were bumper, but late, crops of fruit and vegetables The poliomyelitis season was correspondingly late Whether there was a relationship remains an intriguing question It may be of significance that all the epidemics which have occurred in South Africa, normally a somewhat arid country, have occurred in years of high rainfall.

In another study to determine whether the infection, and not just its paralytic manifestations, was truly seasonal, samples of sewage from a purification plant serving some of the suburbs of Johannesburg were examined at regular monthly intervals for over two years It was apparent in this

tions during the winter and other inter-epidemic periods, and confirms the belief that poliomyelitis is truly seasonal in its incidence

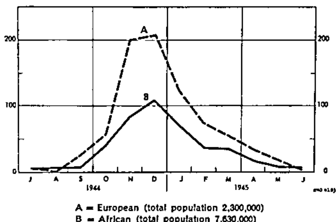
Asia

No attempt will be made to review the incidence of poliomyelitis in all the countries of Asia The reporting of cases is incomplete in most regions, but figures are available which illustrate important trends of the disease in some regions

Palestine

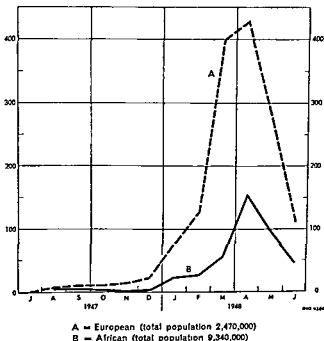
Of the countries of Asia Minor and the Middle East, the situation which has recently developed in Israel is of peculiar interest. Before 1950, wide-

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Ceylon

De Silva[4] has called attention to the increasing incidence of poliomyelitis in Ceylon, an increase noticeable since 1948. The disease tends to occur in the second half of the year, but in 1948 and 1949 the cases were more or less evenly divided between the two halves. The number of cases was high in Colombo in the years with less rainfall and a high humidity.

The incidence of poliomyelitis in Ceylon is still mainly confined to children. The age of 75% of the patients was under three years About 85% of the cases were seen among the poorer classes of Colombo, whose living conditions and sanitation are of a very low standard. De Silva pleads that a more accurate study of the disease as seen in the tropics should be made in Ceylon; such a study would yield most valuable information

Japan

Paul[20] in his detailed study of the occurrence of poliomyelitis in Japan, noted that small epidemics occurred from 1921 onwards Although no serious epidemics have yet been experienced, the average annual mortality is similar to that of the USA Of the diagnosed cases, 70% were in children under 3 years of age, 90% in children under five years of age. This age incidence is similar to that found in other warm climates where sanitation is primitive. Bulbar cases were less common in Japan than in the USA. It appeared to Paul that the disease is in transition from an endemic to an epidemic stage Another transition—the tendency observed in several other countries for the infection to involve older children—has not yet occurred.

Central America

The occurrence of epidemics apparently for the first time has been reported from several countries of Central America

In 1949, in Guatemala, 56 cases with 7 deaths were reported In Mexico, sporadic cases only were reported, with a yearly average of 26 From 1946-9 there was an increasing incidence culminating in the occurrence of 683 cases in 1949 In Panamá, an increasing incidence has been observed since 1947, but from August 1950 to April 1951 the first large outbreak occurred in the city of Panamá Admittance to hospital totalled 133 patients, of whom 9 died The greatest incidence—56%—was in children under two years of age, 81% of the cases occurred in children under five years of age

spread epidemics of poliomyelitis were not known in Palestine. During 1950, 1,600 cases with 154 deaths were notified. This was an incidence of more than one case per 1,000 of the population. The following year, although the number of cases—919 with 127 deaths—was less than in 1950, the disease was of a more serious nature for the case mortality rose from 9.6% to 13.8%. A high epidemic incidence was again evident in 1952, when 851 cases with 116 deaths were recorded.

Such a high epidemic prevalence in such a small area for three consecutive years is most unusual and deserves detailed analysis. Falk,[5] in his observations on the 1950 epidemic, noted that the number of cases increased rapidly from mid-April to reach a peak in June. Only 1% of the cases occurred in the local Arab population, a surprisingly low figure which cannot be attributed entirely to under-reporting since a considerably higher proportion of Arab patients suffering from other diseases are admitted to hospital.

Thirty cases, 7.4% of the total (over 400) treated at the Pediatric Department of the Government Hospital in Haifa, occurred in infants under six months of age, 28% in infants up to one year, 56% up to two years, 73.5% up to three years, and 93% up to five years. The high incidence in infants under six months of age is noteworthy. It suggests that they were born of mothers lacking antibodies against the strain of virus responsible for the epidemic.

India

During the second World War, McAlpine[14] and Illingworth[13] noted that paralytic poliomyelitis was rare in Indian troops, but that cases were common among British soldiers serving in that country. The greatest incidence was observed among officers. This was ascribed at the time to the greater likelihood of officers eating contaminated food in restaurants outside military control. Today, the explanation that officers would be less likely to be immune than men would probably be more favoured.

The Indian delegate[29] to the First International Poliomyelitis Conference, held in 1948, commented that poliomyelitis was sporadic in its incidence and that most cases were seen in their late stages by orthopædic surgeons. In 1951, at the Second International Poliomyelitis Conference, the delegate for India[2] stated that:

> "We thought that we in India were fortunate in having a comparatively low incidence of poliomyelitis. Still, in 1949 we had a spurt in epidemic form. This is the first recognized epidemic in Bombay and some other well known cities in the country. In the city of Bombay in 1949 there were reported 389 cases with 65 deaths. . Ninety per cent of those affected were below the age of five ."

In 1951, among hospitalized persons in the principal towns about 541 cases of poliomyelitis were observed.

Another major epidemic occurred in Malta in November-December 1945 Then in 1950-1 an epidemic unexpectedly appeared in June, reaching its peak in the week ending 26 August In this epidemic the same contrast between the age distribution of cases in the Maltese and in British Service personnel was noted:

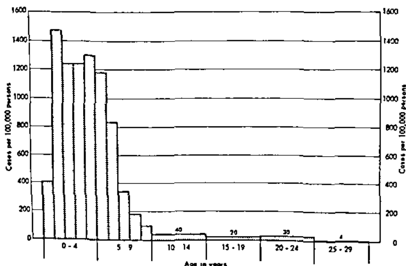
Age-group (years)	Cases *Civilian*	*Service personnel and families*
<1	24	0
1-5	117	7
5-10	13	3
10+	23	42

The more serious and acute cases, and five out of the eight deaths, occurred during the first phase of the epidemic The last phase was characterized by an increased incidence of facial paralysis, a portent—as in previous epidemics—of the end of the outbreak.[8]

Mauritius

Mauritius was affected in its turn early in 1945[15] (see fig. 5) The island is situated in the Indian Ocean, 20°S of the equator. The mean temperature in the mid-summer month of January is 78°F (25 6°C) on

FIG 5 AGE INCIDENCE OF POLIOMYELITIS IN MAURITIUS IN 1945



No attempt will be made to review these outbreaks in detail, but they reveal that the trend of the disease to assume epidemic form, which has been observed in central Africa and in some countries of Asia, has also appeared in the tropical areas of America.

Island communities

A notable feature of the last decade has been the occurrence of severe epidemics affecting island communities. Such epidemics have been reported in the past, but in these recent outbreaks, owing to various circumstances, it has been possible to arrange for detailed epidemiological and clinical studies, and in some of the later outbreaks for immunological and virological studies as well, to be carried out. These studies have been invaluable in emphasizing and elucidating some of the factors concerned in the incidence of paralytic poliomyelitis, and it will be worth while to consider these epidemics in detail

Malta

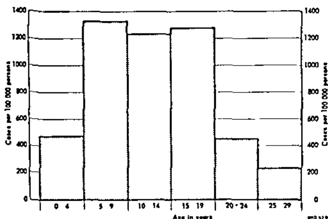
The epidemic of poliomyelitis in Malta in 1942 occurred just after its relief from the prolonged siege, during which most drastic rationing had been introduced and the people of the main island no longer had enough to eat. Soon after the arrival of supplies in November, sent to relieve a situation which had become desperate, the epidemic of poliomyelitis started The epidemic reached its peak in the week beginning 25 December, when there were 108 cases There were 483 cases in all · 426 civilian cases and 57 in the Services Of the 61 adult cases over 20 years of age, only four were Maltese All the Service personnel involved were from the United Kingdom, with a case incidence of 2·5 per 1,000 This incidence was striking since in a number of units Maltese and United Kingdom troops worked together and many other units employed Maltese cooks and labourers The incidence was four times as high in the Royal Air Force as in the Army personnel.[27]

Among the civilians it was noted that the incidence among infants from birth to three months was relatively low. This suggests that some kind of immunity had been transmitted from mother to child. The incidence of the disease then rose to a peak among the two- and three-year-olds, was still high during the fourth and fifth years of age, and then fell rapidly so that from the age of ten upwards, excluding the Services, there were but six cases. It therefore appeared that many children under five years of age, and some under ten years, had failed to become immunized,

extraction ; their ancestors came mainly from the East Indies, West Africa, and Great Britain. Gross overcrowding exists on the island The last ship to call before the onset of the epidemic had previously called at Durban and Cape Town in South Africa, where an epidemic of poliomyelitis had just occurred.

The epidemic, which began in the middle of November, was virtually over by the end of December Within this time 217 cases, of which 11 were fatal and 66 paralytic, occurred One European girl, aged ten, had

FIG. 6. AGE INCIDENCE OF POLIOMYELITIS IN ST. HELENA IN 1945



an abortive infection, all the other cases were islanders No case was detected in an infant under one year of age, and there was a very low incidence in children up to five years of age The brunt of the infection fell on the next three five-year age-groups, with most deaths occurring in the 15-19-year age-group (see fig 6) The number of paralytic cases (66) together with the number of fatal cases (11, or 14 3% of the combined total) gives an attack-rate of 1,920 per 100,000. Two-thirds of the total of 217 cases—an attack-rate of 5,400 per 100,000—were abortive Nissen,[17] who studied this epidemic in detail, concluded that it affected a virgin island population

Such epidemics emphasize certain features which have not been so

the coast and 75°F (23.9°C) on the central plateau; corresponding temperatures in July, the coldest month, are 68°F (20°C) and 64°F (17 8°C) Rainfall varies from 45 inches (115 cm) a year on the coast to 148 inches (375 cm) in the hills; the wettest months are December-April. Three cyclones hit the island in 1945: on 15 January, 2 February, and 7 April The first two caused damage all over the island, while the third affected the south-eastern part only

Most of the dwellings are bamboo huts with thatched roofs and mud floors. Stone and wooden huts, some with corrugated-iron roofs, also exist Overcrowding is very great. Sanitary arrangements are poor all over the island, Port Louis is the only place with a water-carriage system. Most places have unscreened pit latrines, with rickety super-structure; many of these were blown down by the cyclones and until repairs were carried out, weeks or months later, were used less often than usual.

The diet of the majority of the population is very poor by European *standards, protein in particular being deficient*

The curve of the epidemic, which occurred in February, March, and April 1945, was of a symmetrical and somewhat explosive character There were at least 1,018 cases, giving an attack-rate of 2 4 per 1,000 of the population; the case mortality was 6%. The epidemic began in one urban district and spread rapidly all over the island; contact appeared to be the most important factor in the spread of infection.

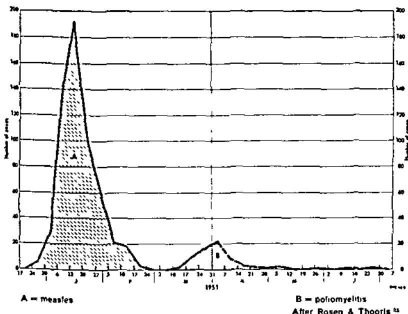
In spite of the inadequacy of the diet, it did not appear that malnutrition determined the incidence of poliomyelitis. There was a high incidence in Chinese children, who enjoyed a more abundant diet than Indian and Creole children

St Helena

The first epidemic of poliomyelitis of which there is any record, curiously enough, occurred in St. Helena early in the 19th century. Sir Charles Bell,[3] in 1836, wrote that "a lady whose husband was an English clergyman at St. Helena consulted me about her child who had one leg much wasted in its growth. She mentioned that an epidemic spread among all the children on the island about 3 or 5 years of age It was afterwards discovered that all the children who had the fever were similarly affected with a want of growth in some part of their body or limbs." The infection must have died out because the disease was unknown on the island within the memory of its oldest inhabitants until towards the end of 1945 when this remote community suffered a severe outbreak.[17]

The climate of St Helena, which lies in the South Atlantic Ocean 16°S and 6°W, is healthy and temperate The islanders are of mixed

FIG. 7. COMPARISON OF MEASLES AND POLIOMYELITIS EPIDEMICS IN TAHITI * IN 1951



* The number of hospitalized cases of measles by week of admission, and the number of cases of paralytic poliomyelitis by week of onset, for the districts comprising the Taravao Medical Post, Tahiti

Rosen & Thooris,[25] who studied this epidemic, recall that in Western Samoa, in 1932, Lambert reported 138 cases of paralytic poliomyelitis among 1,766 children under five years of age—an incidence of 78.1 per 1,000—who had received recent injections of neoarsphenamine No cases were reported in persons of five or more years of age, who had apparently all received the neoarsphenamine intravenously Although its true significance was not fully appreciated at the time, this is one of the first records of the part intramuscular injections play in predisposing the injected limb to paralysis, should the individual be infected or become infected soon after with the virus of poliomyelitis

Features of island epidemics

When these island epidemics are compared, the most notable and significant difference is in the age incidence of the cases

In Malta and Mauritius the disease was essentially infantile. In St Helena and the Nicobar Islands, the disease affected all age-groups—the

As has been noted, Olin [18] considers the changing age-distribution of the disease to be one of the most important factors in determining the increasing number of cases to be seen in such countries as Sweden

Nicobar Islands

In November and December 1947, a severe epidemic occurred in one of the Nicobar Islands [19] The infection was apparently introduced from another island In a population of about 9,000 there were over 800 cases (566 paralytic) with 118 deaths within two months. All age-groups up to the age of 25 years were affected and the majority of cases and of deaths occurred in individuals over six years of age.[16] This obviously was another example of a " virgin soil " epidemic

French Oceania

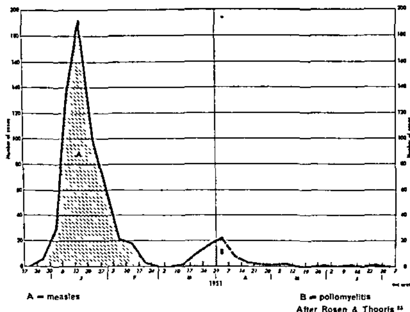
More recently, an illuminating report [25] has described an outbreak of poliomyelitis in French Oceania This territory has a population of about 63,000 inhabitants, the majority of whom are of Polynesian origin. They live mostly in houses of palm fronds and bamboo and wooden-frame construction with corrugated-iron roofing. Overcrowding is almost universal The diet consists of a mixture of the classical Polynesian fare of fish, coco-nuts, taro, bread-fruit, and various imported foodstuffs The water-supply is piped from uninhabited watersheds. Sewage disposal is by a water-carriage system in Papeete and by shallow pit privies in the districts

During the months of March, April, and May 1951, 128 cases of paralytic poliomyelitis were reported from the scattered islands comprising French Oceania A high paralytic-rate of 360 per 100,000 was recorded for Tahiti. In contrast to most epidemics in tropical areas, the attack-rate in the local outbreak for the 0- to 4-year age-group was relatively low and, as in St. Helena, the highest attack-rates occurred in the 11- to 14-year and the 15- to 19-year age-groups.

It was found that children under 15 years of age, who had recently received weekly intramuscular injections, experienced a much higher paralytic attack-rate—81.2 per 1,000—than did the apparently comparable population who had not received injections recently.

This poliomyelitis epidemic was explosive, most cases occurring within a five-week period from 18 March to 21 April When compared with a measles epidemic it seemed that, although clinical manifestations were much less frequent, the infection was disseminated as rapidly (see fig 7) This suggests that, like measles, poliomyelitis in this outbreak was spread by contact rather than as an alimentary infective disease.

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over-five-year-olds more severely than the under-five-year-olds. This difference in behaviour of the epidemic, which was possibly due to the same strain of virus, though this point is uncertain and unfortunately must remain uncertain, is of fundamental importance The most likely explanation seems to be that Malta and Mauritius, though islands, are in the stream of migration and commerce and, until the second World War, had frequent contacts with the outside world and presumably with poliomyelitis virus St Helena and the Nicobar Islands are apart from the general stream of commerce and travel and, in their isolation, the people have grown up out of contact with at least one of the types of poliomyelitis virus, the type responsible for the epidemic

Although, at the time, it was concluded that the epidemics in Malta and Mauritius were due to endemic strains of virus, there is some reason to believe that they, like the epidemics in St Helena and the Nicobar Islands, were due to recently introduced strains of virus. Paralytic infections with the poliomyelitis virus were common among the British troops in the Middle East and it is certain that non-paralytic infections, although unrecognized, were much more prevalent. It is possible that the rapid passage of virus through a large number of susceptibles resulted in the development of a more than usually invasive strain or strains of virus An opportunity also existed for the recombinations of different strains of virus, and this might have resulted in such an invasive strain, though until more is known of this phenomenon its possibility must remain a matter of academic discussion and investigation

Owing to the circumstances of the times, there was abundant opportunity for the dispersal of strains of poliomyelitis virus from the Middle East and other tropical regions. It is clear that these invasive strains were widely disseminated throughout the world during and following the second World War Before the war, the population of Malta acquired immunity without suffering from the paralytic manifestations of the infection to any great extent. Presumably they acquired this immunity from infection with endemic relatively non-invasive strains of virus, which nevertheless were similar antigenically to the strains introduced immediately before the epidemic, so that the immunity acquired was able to resist even the infection of the invasive strain of virus responsible for the epidemic

Factors Determining the Incidence of Poliomyelitis

This survey of poliomyelitis in the under-developed areas of the world has revealed a great diversity in the pattern of the epidemics It now remains to discuss some of the factors which may be responsible for these observed differences, and for the notable changes in pattern which have recently occurred

Racial Incidence of Poliomyelitis

In many countries it has been noted that the incidence of poliomyelitis varies greatly among different races in the same region. In the north-eastern States of the USA, the incidence of paralytic poliomyelitis is four times as great in white children as it is in Negroes, but in the southern States there is little difference. In the Hawaiian epidemic of 1940 the attack-rate was highest in the Caucasian group and lowest in the Filipino. In the San Francisco epidemic of 1930, the attack-rate in the Japanese was the same and in the Chinese twice as high as in the non-orientals

In the epidemic in Mauritius in 1945 the attack-rate was highest in the Chinese and Indians

In South Africa in the epidemics of 1944-5 and 1948 ten times as many cases were notified in Europeans as in the Bantu, the indigenous people of southern Africa The question naturally arises as to whether this is a real difference or one resulting from deficient notification in the more primitive section of the population. In outbreaks in relatively closed mining communities in Northern Rhodesia and Swaziland, where the whole population was under close medical supervision, an even more marked discrepancy in the incidence of the paralytic disease in the two sections of the population was apparent Although the difference may not always be as great as the figures indicate, there is, therefore, little doubt that there is a striking difference in the racial incidence of the disease in some countries It may well be that certain races in or from certain regions of the world are more resistant than others to the paralytic effects of the poliomyelitis virus

Innate resistance of the host is often of decisive importance in determining whether any infection will cause disease or not. It has been possible to develop particular genetic strains of the same species of animal, which are either unusually susceptible or unusually resistant to various experimental infections Perhaps such strains of human beings may develop under natural conditions. In the case of human beings, the relative resistance of the Negro to benign tertian malaria is well known Resistance is shared by Negroes who themselves have never been in a malarious area and may be the result of the elimination of susceptible individuals [illegible]

[illegible]

[illegible]

of descendants of Europeans as compared with Africans to tuberculosis in Africa may have resulted in the same way. The European has been exposed to this infection for generations There is reason to believe that tuberculosis has only invaded many parts of Africa within living memory

This survival of the fittest may account for the apparently greater resistance to paralytic attacks of poliomyelitis of people living under primitive conditions in some parts of the tropics It is likely that under the strict taboos of tribal custom the chance of a man or woman with withered limbs being allowed to perpetuate his kind is not good. In the tropics, where it is now clear poliomyelitis is hyperendemic, those human strains especially prone to paralytic poliomyelitis would thus eventually be eliminated.

In South Africa it has been noted that, although syphilis is rife amongst them, the Bantu are less liable to tabes dorsalis and general paralysis than are the Europeans among whom syphilis is rare. This apparently inherent non-susceptibility of the central nervous system to disease may be of some importance in determining the outcome of an infection with poliomyelitis virus However, almost all authorities will agree with Sabin[26] that a certain way of life has more to do with the incidence of paralytic poliomyelitis than race as such.

Dietetic Factors

It has been shown by several investigators that diet influences the susceptibility of experimental animals to poliomyelitis It has been suggested that the deficient diet of most people in under-developed areas plays some role in determining their relative resistance to paralytic poliomyelitis.

Studies of the "biochemical make-up" of individuals of many under-developed areas in comparison with the standards accepted as normal in individuals in normal health in more developed countries has revealed important and significant differences which appear to be conditioned by their staple cereal diet Many more such studies will be required to assess the meaning of these differences One of the most interesting is the difference in the serum protein levels It is accepted in Western medicine that the serum of [illegible]
and that a rev[illegible]
pathological [illegible]
albumin-globulin ratio is the rule rather than the exception in individuals in many of the tropical and subtropical regions.

Other studies no doubt will reveal other differences. How these differences affect the incidence of infectious disease is not known. It is conceivable that they have a profound effect. However, in the present survey it has been noted that the grossly undernourished infants of Malta, the undernourished population of St. Helena, as well as the well-fed Swedes, Danes, and North Americans, are all liable to severe epidemics of polio-

myelitis It thus emerges that the diet—whether causing undernutrition, overnutrition, or malnutrition—cannot have a decisive influence on the incidence of paralytic poliomyelitis

Immunity Status[10]

It is now becoming clear that the factor of greatest importance in determining the incidence of paralytic poliomyelitis is the state of immunity of the affected population This factor is considered in detail in other contributions to this monograph,* and only certain aspects relevant to the present survey are considered here

Passive immunity

Passive immunity is transmitted from mother to offspring in man, apes, and rodents predominantly via the placenta When they are born, human babies have a full complement of their mothers' antibodies Studies both in poliomyelitis and in diphtheria, where the antibody content is relatively easy to measure, have shown that these antibodies fall off in titre progressively after birth until they are no longer demonstrable at about the sixth to the ninth month It has been found that this passively acquired immunity often interferes with active immunization against diphtheria and smallpox.

Active immunity

Presumably there comes a stage of balance between the infecting virus and the passive immunity when minimal but active infection occurs Exposure to the virus of poliomyelitis during this stage might result in a silent but immunizing infection.

Milk from immune mothers also contains antibody to poliomyelitis virus and it is possible that infection occurring under " cover " of mothers' milk will tend to be mild and therefore non-paralytic Experiments in cynomolgus monkeys have failed to demonstrate that the drinking of antipoliomyelitis milk can prevent the paralytic consequences of infection It is still possible that in human beings the consumption of larger amounts of milk and smaller amounts of virus may serve to diminish the incidence of paralytic infection during breast feeding Infections occurring so early in life are more likely to develop among infants in environments where the virus is widely disseminated The mothers in such environments are also more likely to have a high concentration of antibody

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* See pages 297, 335, and 357

Little work has been done in studying the incidence of infection at these times in an infant's life In one investigation, Gear et al [12] have observed a group of Bantu babies living in slum conditions in a township possessing purified water but no water-borne sewerage These babies have been tested at regular intervals for the presence of poliomyelitis virus. Beginning within 14 days of birth, tests have been carried out at monthly intervals Some of the babies have now been under continual observation for five years Of the 16 babies who remained under observation for the first full year of study, none showed any signs or symptoms suggestive of poliomyelitis; it was proved, however, that 4 (25%) of the 16 had been infected with the virus of poliomyelitis during that time. One contracted the infection in its third month, one in its eighth month, and two in their twelfth month The virus isolated from the infant in its third month proved not to be of the Lansing type, and the infant, subsequent to the infection, did not develop Lansing antibodies. The other three infections all took place in the same month of the year (October 1949), they were due to a Lansing type of virus and the infection was followed by the development of Lansing antibodies. At the time of infection the babies were still being nursed by their mothers, all of whom had Lansing antibodies in their blood.

It is clear from these observations that infection may take place in a considerable proportion of infants during the first year of life when they are still being breastfed by immune mothers. It is not clear to what extent these babies were protected from the paralytic consequences of infection by this nursing Evidence was also obtained, by direct isolation of the virus and by the demonstration of the development of antibodies, that several of the babies who had not been infected whilst being breastfed were later infected successively with all of the three known types of poliomyelitis virus. None were ill at the time of these infections Subsequent to the infection, it was shown that they had developed the corresponding antibody.

In primitive communities, where faecal infection is widespread, the virus must often be subjected to aging and drying before infecting a new host It is tempting to suggest that this natural application of Pasteurian principles results in some attenuation of its virulence and that this to some extent accounts for the fewer paralytic cases seen in such areas However, the strains of virus mentioned above, isolated from Bantu babies by Gear et al, were highly virulent for monkeys and remained so in the few passages made. Similarly, the severe infections suffered by American soldiers in certain tropical areas do not suggest any attenuation of the virulence of the virus in these areas.

Serum antibody surveys

Support for the theory that latent immunization is responsible for the relative immunity of many people and its lack for the greater susceptibility

of others has been forthcoming from the results of serum surveys. In one of the earliest of these, Paul & Trask[22] observed that the sera from persons from tropical countries contained a higher percentage of antibodies to the MV and Aycock strains than sera from the temperate zones

The adaption of the Lansing strain of virus to mice by Armstrong[1] made large-scale surveys of sera possible and these have been undertaken in most regions of the world In Baltimore, Turner et al[29] showed that 72% of infants under three months of age showed Lansing antibodies, presumably passively acquired from their mothers At one year of age, the proportion with positive protection had declined to 10%. The proportion then rose progressively until, at the age of 15 and over, 89% had acquired these antibodies Turner et al. noted further that the acquisition of antibodies was greatest in the autumn and corresponded with the poliomyelitis season.

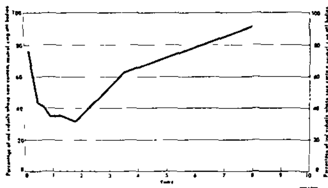


FIG 8. LANSING ANTIBODIES IN BANTU INFANTS

The age distribution of Lansing antibodies has been studied in several other regions (see fig 8). It emerges that the age at which these are acquired varies greatly in different parts of the world. As a general rule, except in isolated communities, the more primitive the hygiene and sanitation the earlier they are acquired, and conversely, the higher the standard of living the later they are acquired by the majority of individuals. It has also been noted that the average age at which clinical poliomyelitis usually develops in a given population is often the same as the average age at which Lansing antibodies are acquired The determination of Lansing antibody titre i

poliomyelitis in

not related to th

also to reflect, in a general way, the immunity to be expected to the other types of virus It can be readily understood that this is not always so.

However, now that it is possible to carry out protection tests in tissue culture against the other types of poliovirus, great clarification of the epidemiological picture in many parts of the world is to be expected. Such surveys as have already been carried out have revealed that where the Lansing virus is widely disseminated the other types of virus are also widely disseminated Much more work along these lines remains to be done, but it soon may be possible to determine accurately the state of immunity of a population and to forecast accurately the course of poliomyelitis epidemics Such information will be invaluable to those concerned with public health

From such surveys as have already been carried out, it becomes clear that in certain tropical areas where poliomyelitis had previously been thought to be rare, the infection is widespread, even hyperendemic, and that all of the known types of poliomyelitis virus are prevalent. Indeed, there are some reasons for believing that poliomyelitis is essentially a tropical disease and that from the reservoir of virus in the tropics the infection ebbs and flows in the wake of the summer into temperate regions north and south of the Equator In this regard it will be of crucial importance to determine whether epidemics in such countries as the USA result from the steady northward migration of infection which seems to occur, or whether they are due to the progressive activation of virus already present. Both processes may operate on different occasions, but further study of the migration of infection is required before an answer to this intriguing question can be expected.

Virus Types in the Tropics

From surveys of immunity of sera from individuals in the tropics, it is clear that all the three known types of poliomyelitis virus are prevalent Little has yet been published of the results of typing virus isolated in these regions In one study carried out by Malherbe, Harwin & Michaelis in the Laboratories of the Poliomyelitis Research Foundation, South African Institute for Medical Research, Johannesburg, Union of South Africa, viruses isolated from cases and outbreaks in various territories of central Africa, as well as strains isolated in the Union of South Africa, were typed. The results are shown in table III.

It is of interest to note that the isolations from cases made in 1947, 1948, 1949, and 1951 were all type 1 Brunhilde-like viruses. To these may be added the three type 2 viruses isolated by Gear et al.[12] from Bantu babies with *silent infections In 1952 and 1953, more type 2 and type 3* than type 1 strains were identified. It is difficult to know whether these findings reflect the true distribution of strains in these years and

TABLE III. TYPES OF POLIOMYELITIS VIRUS ISOLATED IN SOUTHERN AFRICA

Number	Date	Place	Origin	Virus type
1	XI 1947	Swaziland	silent infection	1 Brunhilde
2	V 1948	Johannesburg, Union of South Africa	sewage	1 "
3	1949	Nairobi, Kenya	septic-tank effluent	1 "
4	VI 1950	Nyasaland	stool of paralytic case	1 "
5	X 1950	"	"	1 "
6	VII 1951	Boksburg, Union of South Africa	"	1 "
7	X 1951	Salisbury, Southern Rhodesia	"	1 "
8	X 1951	"	"	1 "
9	XI 1951	"	"	1 "
"	"	"	associate of two fatal cases (father and mother)	1 "
10	III 1952	"	stool of paralytic case	1 "
11	IV 1952	"	"	1 "
12	VI 1952	"	"	1 "
13	XII 1952	"	"	2 Lansing
14	III 1952	Johannesburg, Union of South Africa	"	1 Brunhilde
15	VI 1952	Germiston, Union of South Africa	silent infection	1 "
16	X 1952	Cape Town, Union of South Africa	central-nervous-system fatal case	2 Lansing
17	I 1953	Boksburg, Union of South Africa	stool of paralytic case	1 Brunhilde
18	III 1953	"	"	1 "
19	I 1953	Evaton, Union of South Africa	"	1 "
20	III 1953	Johannesburg Nursery School, Union of South Africa	stool of contacts (25 virus isolated, 8 typed)	3 Leon
21	III 1953	Johannesburg, Union of South Africa	stool of paralytic case	3 "
22	III 1953	"	"	1 Brunhilde
23	IV 1953	"	"	3 Leon
24	III 1953	East London, Union of South Africa	"	2 Lansing
25	VIII 1953	"	"	2 "
26	IV 1953	Johannesburg, Union of South Africa	"	3 Leon
27	IV 1953	"	"	1 Brunhilde
28	V 1953	"	"	1 "
29	VI 1953	"	stool of contact	1 "
30	X 1953	"	stool of paralytic case	3 Leon
31	XI 1953	"	"	3 "
32	XI 1953	"	stool of contact of No 31	3 "
33	XII 1953	"	stool of paralytic case	2 Lansing
34	VI 1953	Salisbury, Southern Rhodesia	"	2 "
35	IX 1953	"	"	2 "
36	XII 1953	Cape Town, Union of South Africa	"	3 Leon

Total type 1 (Brunhilde), 22 strains, type 2 (Lansing), 7 strains, type 3 (Leon), 8 strains

attempted in southern Africa before the tissue-culture method of isolation was introduced It is also of interest to note that Brunhilde, Leon, and Lansing virus were prevalent in southern Africa in 1953, a non-epidemic year.

It will be of considerable value to know whether most cases in an epidemic are caused by one strain or one type of virus, or whether during epidemics more than one type is responsible for many cases. Future virus-typing studies in parallel with antibody studies should shed light on this problem

Future Developments

Great changes in the way of life of millions of persons in Africa, in Asia, and in tropical America are taking place and impending Schemes to house slum dwellers and those of their country cousins still to be attracted to the towns and cities, are being implemented For the first time large sections of the population are being provided with purified water as well as with water-borne sewerage, greater numbers will be provided with these amenities in the near future It may be asked what will happen when the African and other individuals from primitive surroundings drink pure water and eat safe food not exposed to flies There is little doubt that the incidence of summer diarrhoea and dysentery will fall precipitously The infant mortality-rate, so appallingly high at present, will fall in parallel There also seems to be little doubt that the incidence of paralytic poliomyelitis will rise and that this trend will continue until some means of prevention is found.

Conclusions

From this survey it appears that the most significant difference between the occurrence of poliomyelitis in the well developed countries of the temperate zone and the less developed areas of the tropics, and elsewhere, is no longer so much the difference in incidence, although this is still great, but in the distribution of cases in the various age-groups

In those regions where poliomyelitis is endemic or hyperendemic, the great majority of cases occur in the younger age-groups and often over 90% occur in infants under five years of age. Where the disease is endemic, but opportunities for wide dissemination of the infection are limited, a large proportion of individuals escape infection under the age of five, only to fall victims when older. Where the infection has been absent for a generation or more, the introduction of an invasive strain of poliomyelitis virus results in a severe epidemic involving the older age-groups more severely than the one-to-five-year age-group

As with most infectious diseases, poliomyelitis tends to be less severe in young children than in older children and adults and, being less severe, is less likely to cause paralysis. Consequently, in those countries where the

age of infection is delayed, the number of cases of paralytic poliomyelitis increases greatly.

In this respect poliomyelitis does not form a contrast to other infective diseases, as may seem to be the case. Actually the situation conforms with that in other diseases which tend to be hyperendemic in some areas of the world and not in others Perhaps the clearest example of these is malaria. In those regions of the world where malaria is hyperendemic, clinical manifestations of illness in the older age-groups of the indigenous population are rare and epidemics are almost unknown. However, when people who have had no previous experience of malaria come into such areas they suffer severely In those regions where conditions are only occasionally suitable for the transmission of infection, the population suffers from epidemics when these conditions arise. Between the hyperendemic and non-malarious areas there are various intermediate situations, whose characteristics depend largely on the state of immunity of the population which, in turn, is determined by the frequency of infection. Similarly, in the case of poliomyelitis, there is now little doubt that the age distribution of cases reflects the state of immunity of the population Where the infection is hyperendemic—as in most of the under-developed areas of the world—the infants are affected but the older age-groups are spared. Where the infection is introduced into a community which for a generation has been free from it, all age-groups, and particularly the older children and young adults, are severely affected Between these two extremes all intermediate grades of pattern are to be found

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INCIDENCE OF POLIOMYELITIS SINCE 1920

MATTHIEU-JEAN FREYCHE, M D.

JOHANNES NIELSEN, cand. polit.

Division of Epidemiological and Health Statistical Services, World Health Organization, Geneva

If, like Burnet, we believe that " the only practicable method of treating the available data about the prevalence of disease is statistical ",[5] we are justified in attempting to apply statistical analysis to the official figures available on cases of poliomyelitis and deaths due to this disease in the various countries of the world However, the inherent difficulty of such an undertaking is obvious In certain countries, only cases of the acute paralytic form of the complaint are registered under the heading of " poliomyelitis " , in addition, even in the most carefully compiled series, diagnostic errors of the order of 14% have been found [8] Elsewhere, notifications also cover a varying proportion of febrile states with signs of meningeal irritation, without symptoms of spinal or bulbar paralysis, and perhaps abortive forms without manifestations which can be ascribed to involvement of the central nervous system In such cases a clinical diagnosis can only be one of probability, even when it refers to patients who have been in close contact with a confirmed case of poliomyelitis, and the possibility of error is very large However, in view of the practical impossibility of any laboratory confirmation, it is probable that the immense majority of such clinical cases are not notified to the health authorities. The same applies in even stronger measure to the innumerable asymptomatic infections, which escape all medical control

Such sources of error and variability considerably limit the value of the statistical data published, even in those countries where the most satisfactory health and social conditions are to be found Furthermore, the comparability of the available data is also affected by the disparity of national legislations and of statutory and administrative provisions applying to the notification and registration of cases, by the uneven distribution of physicians between urban and rural areas, by the greater or lesser degree of co-operation on the part of the medical profession in establishing accurate

statistics, and even by the presence or absence of the concept of "epidemic". Later on we shall return to this particular point. In practice it must be recognized that, in relation to the real incidence of clinical poliomyelitis, the proportion of notifications by the medical profession certainly varies from one country to another—even from one region to another in the same country—and depends on factors such as the interest shown by physicians in poliomyelitis, or the fear inspired in the public by this disease.

Consequently, any study of the official morbidity and even mortality statistics for poliomyelitis in the world as a whole must be limited, as things are at present, to the consideration of very general points of view. For most countries no information is available, and for many others the information existing must be treated with caution A certain number of countries have instituted a relatively uniform system for registration of clinical cases, but many publish only the total number of medical notifications, and no data on the distribution of cases by age, sex, etc. However, for several years a few countries have endeavoured to distinguish between "paralytic" and "non-paralytic" cases, even anticipating in some instances the resolution whereby, in 1950, the Third World Health Assembly requested the Director-General of WHO, pursuant to articles 23 and 64 of the constitution, "to urge national health-administrations to state separately the number of paretic cases and of non-paretic cases when reporting on poliomyelitis".[30] Nevertheless, the number of countries applying these rules is still limited, moreover, in the absence of internationally defined criteria, "border-line" cases with more or less severe but transitory symptoms of involvement of the central nervous system are classified in a variable manner, depending on the national and perhaps even the local practice

Epidemicity

"The transformation of the relatively uncommon 'infantile paralysis' of the 19th century into 'epidemic poliomyelitis' of almost worldwide distribution presents today one of the most formidable public-health problems "[32]

The Stockholm epidemic of 1887, described by Medin,[21] appeared in fact to be the prelude to a series of other epidemic outbreaks which, in the first years of the 20th century, affected first Sweden and Norway (1905) and then, almost simultaneously, the State of New York (1907), Alaska (1908), Minnesota, British Columbia, Alberta (1910), etc [17, 18, 26, 29] It seemed as if this were a new disease, spreading from the Scandinavian peninsula and covering the northern parts of Europe and North America (poliomyelitis "belt"[2]). In any case, from about 1920 onwards poliomyelitis epidemics have occurred with increasing severity, not only in the countries mentioned above, but generally in all countries where

hygiene and social conditions, judging by criteria such as infant mortality-rates from all causes, may be considered as the most satisfactory. At the same time, these epidemics have tended to affect higher and higher age-groups. In addition, the progressive inclusion of poliomyelitis among the notifiable diseases has shown, despite the imperfections of the morbidity statistics, that the disease is much more frequent in tropical countries than is generally believed,[4, 9, 11, 28, 31, 33] (see also page 31 of this monograph) although epidemic outbreaks in such regions are probably more limited and rarer than in areas with a higher standard of living.[21]

Numerous immunological and virological investigations, which it is impossible to summarize here, have shown that endemic poliomyelitis is prevalent among all the peoples of the world.

The theory of the appearance, towards the end of the 19th century, of new strains of virus with increased pathogenicity would make it possible to explain the increased incidence of the disease. However, it is perhaps unnecessary to call on such a hypothesis. The existence of authentic paralytic poliomyelitis epidemics not only in islands such as St Helena,[3] but also in continental regions such as Louisiana,[7] or Brazil,[1] is proved by very old sources. The first epidemics described in the Scandinavian countries, North America, Australia, and New Zealand were all characterized by the classical clinical picture of "infantile paralysis", children under five being by far those most frequently attacked.[5, 6, 27] Such a distribution leads to the supposition that older persons were protected by an already widespread immunity, which implies longstanding endemicity. The existence of local strains, perfectly capable of causing paralysis among newly arrived persons, has been demonstrated during the past ten years in the Eastern Mediterranean, India, the Philippines, etc., by the fact that troops coming from temperate regions have suffered much more from poliomyelitis than troops recruited on the spot.[25] A similar exceptionally high incidence of poliomyelitis among immigrants has been observed in many other places (North Africa, Rhodesia, Angola, Mozambique, Bombay, Singapore, Bangkok, Japan, Korea, etc.).[33]

As a result of such observations among many others, the general belief today is that there is no fundamental difference between the epidemiology of poliomyelitis and that of the other endemo-epidemic diseases most widespread all over the world. This concept is dealt with in two other articles in this monograph (see pages 9 and 31).

Seasonal Distribution

Except in the tropical countries, where hyperendemic outbreaks may occur at any season, the highest incidence is usually reached between the months of August and October in the countries of the northern hemisphere,

and six months later in the countries of the southern hemisphere. However, numerous purely winter epidemics have been observed in various countries.[11] In Australia, a tendency for the prolongation of epidemics throughout the winter has been shown for a certain number of years.[5] So far, no convincing explanation has been given for this seasonal distribution.

Spontaneous Localization of Epidemics

The patchy nature of poliomyelitis epidemics, their spontaneous limitation, and their irregular return, are features hardly apparent in the national morbidity statistics which are studied here. These outbreaks must doubtless be considered as the visible clinical and more or less measurable expression of a subjacent phenomenon, namely, the invisible spread of the various virus strains throughout the community. According to the invasiveness and pathogenicity of the virus or viruses concerned, the state of immunity or receptivity of the population considered, and social factors which can favour or impede its spread, the epidemic will be mild or serious, brief or lengthy Sometimes there will be no epidemic.[12] Attempts have been made by various methods to assess the extent of this silent propagation and to determine whether its currents are " wide " or " narrow ", etc , but this need not be enlarged upon here

Trends in Incidence

For the purposes of the following study, official data, as far as available for the past 20 or 30 years, on the number of cases and deaths attributable to poliomyelitis, have been examined separately for each country. During this period the incidence of the disease has shown a general tendency to increase in most countries, however, this tendency has been irregular, epidemic years being separated by periods of relative quiescence of variable duration On the other hand, poliomyelitis mortality has not increased to the same extent.

Europe

United Kingdom, and Republic of Ireland: In *England and Wales* the number of notified cases remained relatively constant from 1913 up to 1946, apart from the years 1926 and 1938, with the rates of 3.3 and 3 8 notifications per 100,000 inhabitants respectively, i e., about twice the rate for this period. In the middle of June 1947, notifications began to increase considerably, although in previous years a seasonal increase occurred only at the end of July. The 1947 epidemic spread rapidly: notifications for the whole year reached 18 1 per 100,000 inhabitants—the highest

figure which has so far been recorded In each succeeding year the number of notifications was higher than that for the years preceding 1947, the rates for 1949 and 1950 in particular reaching 13.7 and 17 6 per 100,000 inhabitants (see fig. 1).

Fig. 1 also shows the number of deaths recorded per 100,000 inhabitants. This number remained fairly constant from year to year up to 1947, when a sudden increase was noted, parallel to the increase in notifications.

In *Scotland*, the incidence of poliomyelitis was of the same order as in England and Wales, with more marked annual variation (see fig. 1). 1928 was an epidemic year (5 7 notifications per 100,000 inhabitants) Relatively high figures were also reported in 1933, 1936, 1938, 1940, 1941, and 1944 (from three to four cases per 100,000 inhabitants). The 1947 epidemic was more serious than in England and Wales, notifications reaching 27 7 per 100,000 inhabitants The year 1950 saw an outbreak of almost equal importance, with a notification-rate of 21 8, although the rates for the inter-epidemic years were considerably below those of England and Wales

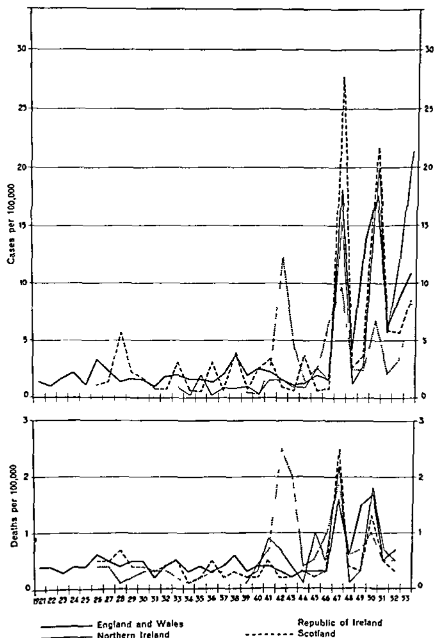
In *Northern Ireland*, poliomyelitis incidence has generally been lower than in Scotland, or in England and Wales. The incidence increased considerably in 1947, 1950, and 1953, with 15 4, 19 9, and 21.4 cases respectively per 100,000 inhabitants.

For the *Republic of Ireland*, official statistics concerning poliomyelitis have been published only from 1939. In 1942 a severe epidemic outbreak occurred, with 12 2 notifications per 100,000 inhabitants. This epidemic, the most serious which had so far been observed, led to a mortality-rate of 2 5 per 100,000 inhabitants, the case-fatality-rate for the disease thus being about 20%

Before 1947, it is not possible to find any similarity in the variation from year to year in the incidence of poliomyelitis in Great Britain and Ireland In that year, however, each of the four territories mentioned above experienced an abnormally high incidence. Since then the annual fluctuations in notifications and deaths have, broadly speaking, been much similar.

Northern Europe In Northern Europe, the incidence of poliomyelitis in general has been higher than in the United Kingdom In *Denmark*, the first epidemic of poliomyelitis was recorded in 1911 In 1934, a violent epidemic broke out with 129 cases notified per 100,000 inhabitants. It affected especially a few districts in south Jutland, and the disease took a particularly mild form (the case-fatality-rate was only 2 3%) Other outbreaks were observed in 1937, 1942, 1944, and 1950, with more than 30 notifications per 100,000 inhabitants in each of these years The most serious epidemic was that of 1952 when 131.7 cases were recorded per 100,000 inhabitants, and almost half of them were of the paralytic type.

FIG. 1. ANNUAL RATES PER 100,000 POPULATION OF NOTIFIED CASES OF, AND DEATHS FROM, POLIOMYELITIS: ENGLAND AND WALES, SCOTLAND, NORTHERN IRELAND, AND REPUBLIC OF IRELAND, 1921-53



An epidemic occurred in *Norway* in 1905 with a notification-rate of 44.2 per 100,000 inhabitants and a case-fatality-rate of 10.4%. In 1911, another severe outbreak occurred with 76.3 notifications per 100,000 inhabitants, with a case-fatality-rate of 15.4%. In 1925, 1936, 1941, 1945, 1946, and in each of the years 1950-3, the notification-rates exceeded 20 per 100,000 inhabitants. As can be seen from fig. 2, each epidemic since 1921 has in general been more extensive than the preceding one, and there has also been a continually increasing number of notifications in the inter-epidemic years.

In *Sweden*, there were severe poliomyelitis outbreaks in 1905 and during the years 1911-3. The notification and case-fatality-rates are given below:

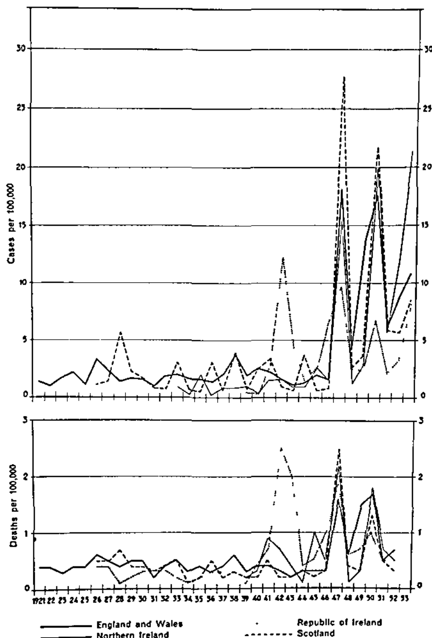
	Number of cases notified per 100,000 population	*Case-fatality-rate (%)*
1905	22.7	11.2
1911	69.6	17.2
1912	73.7	15.4
1913	21.7	18.9

During the first World War and the years following it, the notification-rate in Sweden, as in most European countries, remained relatively low. Since 1924, however, it has reached or exceeded 10 per 100,000 inhabitants, with particularly high figures during the periods 1936-8 and 1943-5 as well as in 1949 and 1950 (see fig 2) The year 1953 experienced the most serious epidemic observed since 1912, the notification-rate reaching 70.9 per 100,000 inhabitants. The annual fluctuations are less pronounced in Sweden than in Denmark or Norway

The disease in *Finland* is characterized by an incidence apparently lower than that in the other countries of northern Europe Since 1940, in almost every year, the notification-rate in Finland has been lower than in the other countries of the region

Fig 2 shows the high level of poliomyelitis incidence in northern Europe as reflected by official statistics It can be seen that epidemic outbreaks, which appeared very irregularly, did not occur simultaneously in the various countries of the region However, for some of the years in the period considered, the epidemic tendency was similar the four countries were affected by outbreaks of poliomyelitis in 1929, 1932, and 1934, as well as in 1944-5 These findings may be explained by the fact that epidemic poliomyelitis generally spreads by means of localized outbreaks of varying geographical extent; although the barriers to such outbreaks represented by the frontiers frequently seem more or less permeable, there can nevertheless be no doubt as to their effectiveness. Consequently, in Europe the territories affected have often remained relatively limited in area, a severe

FIG. 1. ANNUAL RATES PER 100,000 POPULATION OF NOTIFIED CASES OF, AND DEATHS FROM, POLIOMYELITIS: ENGLAND AND WALES, SCOTLAND, NORTHERN IRELAND, AND REPUBLIC OF IRELAND, 1921-53



An epidemic occurred in *Norway* in 1905 with a notification-rate of 44 2 per 100,000 inhabitants and a case-fatality-rate of 10.4% In 1911, another severe outbreak occurred with 76 3 notifications per 100,000 inhabitants, with a case-fatality-rate of 15.4%. In 1925, 1936, 1941, 1945, 1946, and in each of the years 1950-3, the notification-rates exceeded 20 per 100,000 inhabitants. As can be seen from fig. 2, each epidemic since 1921 has in general been more extensive than the preceding one, and there has also been a continually increasing number of notifications in the inter-epidemic years.

In *Sweden*, there were severe poliomyelitis outbreaks in 1905 and during the years 1911-3. The notification and case-fatality-rates are given below ·

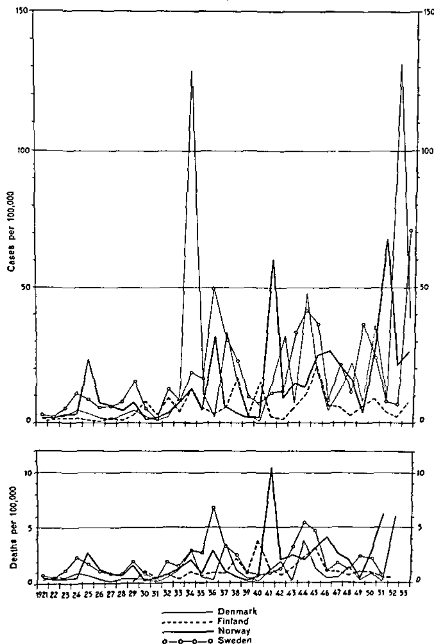
	Number of cases notified per 100,000 population	*Case-fatality-rate (%)*
1905	22 7	11 2
1911	69 6	17 2
1912	73 7	15 4
1913	21.7	18 9

During the first World War and the years following it, the notification-rate in Sweden, as in most European countries, remained relatively low. Since 1924, however, it has reached or exceeded 10 per 100,000 inhabitants, with particularly high figures during the periods 1936-8 and 1943-5 as well as in 1949 and 1950 (see fig 2). The year 1953 experienced the most serious epidemic observed since 1912, the notification-rate reaching 70 9 per 100,000 inhabitants The annual fluctuations are less pronounced in Sweden than in Denmark or Norway

The disease in *Finland* is characterized by an incidence apparently lower than that in the other countries of northern Europe. Since 1940, in almost every year, the notification-rate in Finland has been lower than in the other countries of the region

Fig 2 shows the high level of poliomyelitis incidence in northern Europe as reflected by official statistics It can be seen that epidemic outbreaks, which appeared very irregularly, did not occur simultaneously in the various countries of the region However, for some of the years in the period considered, the epidemic tendency was similar the four countries were affected by outbreaks of poliomyelitis in 1929, 1932, and 1934, as well as in 1944-5. These findings may be explained by the fact that epidemic poliomyelitis generally spreads by means of localized outbreaks of varying geographical extent ; although the barriers to such outbreaks represented by the frontiers frequently seem more or less permeable, there can nevertheless be no doubt as to their effectiveness. Consequently, in Europe the territories affected have often remained relatively limited in area , a severe

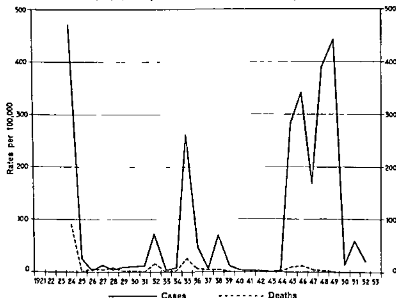
FIG. 2. ANNUAL RATES PER 100,000 POPULATION OF NOTIFIED CASES OF, AND DEATHS FROM, POLIOMYELITIS: DENMARK, FINLAND, NORWAY, AND SWEDEN, 1921-53



epidemic has rarely occurred there in two consecutive years, but this rule is far from being without exceptions

There have been some extremely serious epidemics in *Iceland.* In 1924 nearly 500 per 100,000 population were affected; other extensive outbreaks occurred in 1932, 1935, and 1938 Only a few cases were recorded between 1940 and 1944, and in 1943 the disease seemed to have disappeared. In 1944 and 1945, however, the incidence rapidly increased and in the years

FIG. 3. ANNUAL RATES PER 100,000 POPULATION OF NOTIFIED CASES OF, AND DEATHS FROM, POLIOMYELITIS: ICELAND, 1924-52



1945-9 the notification-rates were higher than are known for any other country in the world In 1946-7, poliomyelitis reached its maximum in December and lasted until the following spring, thus affording a rather exceptional example of a winter epidemic. Fig 3 shows the trend of the notification- and mortality-rates per 100,000 inhabitants for Iceland since 1924 (in which year official figures were first published) The case-fatality-rate shows a tendency to decrease from one epidemic to another The actual figures for the notifications and the case-fatality-rates 1924-51 are given in table I

This table clearly shows that the epidemics developing since 1938 have been of a particularly mild nature, and indicates the progressive reduction in the case-fatality-rate during the period under consideration

TABLE I. ICELAND: REPORTED NUMBER OF CASES OF POLIOMYELITIS, AND CASE-FATALITY-RATES (1924-51)

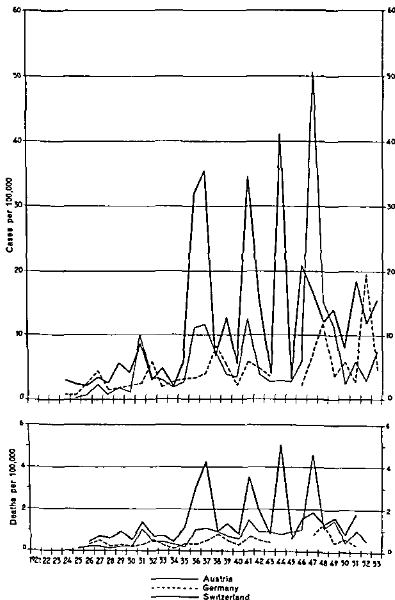
	Number of cases	Deaths per 100 cases
1924	463	19 2
1925	26	0
1926	2	—
1927	12	25 0
1928	4	—
1929	8	12 5
1930	9	11 1
1931	11	0
1932	81	18 5
1933	3	0
1934	7	14.3
1935	300	9 7
1936	53	9 4
1937	5	40 0
1938	81	3 7
1939	12	0
1940	3	0
1941	1	0
1942	1	0
1943	—	—
1944	2	50 0
1945	368	2 7
1946	450	2 9
1947	227	2.2
1948	538	0 4
1949	622	0
1950	17	5 9
1951	85	0

Central Europe Notification of poliomyelitis cases was made compulsory in *Germany* after 1909, in which year a serious epidemic was noted for the first time Incidence in Germany has been very much below that in the Scandinavian countries; the number of cases officially recorded, however, has shown a distinct tendency to increase over the past 30 years. Fig. 4 indicates the trend of incidence for Germany up to 1943 and for the Federal Republic from 1946. Data for the years 1944 and 1945 are lacking. Epidemic outbreaks generally occurred at intervals of three to five years, each epidemic being more serious than the preceding one and inter-epidemic incidence tending to increase. In 1926-7, 1938-9, and 1947-8 epidemic outbreaks succeeded one another with an interval of only one year. During the recent war and in the early postwar years, poliomyelitis incidence seems to have been relatively low; the same phenomenon was noted during the first World War and the years immediately thereafter. It is possible that during these two periods the official statistics were less reliable than in normal times.

In 1947 Berlin experienced its most severe epidemic. The notification-rate reached 76.9 per 100,000 inhabitants; the four Occupation Sectors were all affected to more or less the same extent.

Up to 1947 the official statistics for *Austria* show notification-rates above 10 cases per 100,000 inhabitants only in 1931, 1936, 1937, and 1941.

FIG. 4. ANNUAL RATES PER 100,000 POPULATION OF NOTIFIED CASES OF, AND DEATHS FROM, POLIOMYELITIS: AUSTRIA, GERMANY, AND SWITZERLAND, 1924-53



From 1942 to 1945 the average annual notification-rate was about three cases In 1947 a severe epidemic occurred, with 50 6 cases notified per 100,000 inhabitants, and a case-fatality-rate of 9%. Since then, the incidence has gradually decreased.

Until 1935 poliomyelitis was relatively uncommon in *Switzerland* (see fig 4). After that year, serious epidemics developed in 1936, 1937, 1941, and 1944, with 30-40 cases recorded per 100,000 inhabitants. Since 1946, however, the annual notification-rate has become relatively steady at around 15.

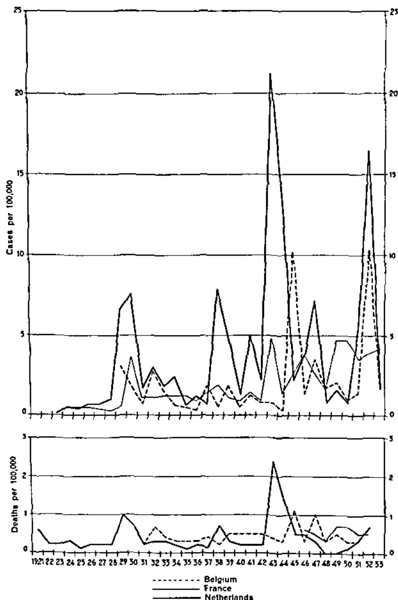
In *Hungary*, the notification-rate before the war was almost as high as in Austria. In 1940-2 it was close to 10 per 100,000 inhabitants ; in 1947 a still more marked outbreak was recorded No information is available for recent years. In *Romania* and *Bulgaria*, during the period for which figures are available (1927-46 and 1927-49 respectively), the number of notifications was considerable. This is also true of *Czechoslovakia*, where a serious epidemic developed in 1948, with nearly 20 cases per 100,000 inhabitants

On the other hand, the number of officially recorded cases in *Poland* and *Yugoslavia* has remained small

Western Europe : In the *Netherlands*, *Belgium*, and *France*, the incidence of poliomyelitis has generally remained below that in northern and central Europe, especially during the period following the second World War (see fig 5). The most extensive epidemics have occurred in the *Netherlands*, but even in this country the notification-rate exceeded 10 per 100,000 inhabitants only in three years (1943, 1944, and 1952) The annual fluctuations have been considerable ; the same applies to *Belgium*, where the *relatively low incidence has shown no tendency to increase since 1929*, except in 1945 and 1952, when rates of about 10 per 100,000 inhabitants were recorded Neglecting the difference in the rates, it is clear from fig 5 that the trend of poliomyelitis incidence is very similar in the Netherlands and Belgium ; apart from the 1945 epidemic in Belgium, the annual fluctuations in the two countries have shown a remarkable similarity since 1939 In *France*, the annual variations in incidence are less marked There has been no major epidemic affecting the country as a whole, but since 1943 the *notification-rate* has been at a higher level than in the prewar period.

Southern Europe Among the countries of southern Europe, poliomyelitis—*as far as can be judged from the number of notifications—is* particularly frequent in *Italy*. After a long period of low notification-rates, more than five cases per 100,000 inhabitants were recorded in each of the years 1936-1941, reaching the figure of 13.7 in 1939 During the years which followed, the notification-rate gradually decreased, becoming stabilized at between five and six from 1945 onwards, with a severe outbreak

FIG. 5. ANNUAL RATES PER 100,000 POPULATION OF NOTIFIED CASES OF, AND DEATHS FROM, POLIOMYELITIS: BELGIUM, FRANCE, AND NETHERLANDS, 1921-53



in 1953. Mortality due to poliomyelitis has tended to decrease since 1921, despite the increase in the number of cases notified.

Spain and *Portugal*, for which poliomyelitis statistics are available only for the past 10-15 years, show notification-rates in the neighbourhood of two per 100,000 inhabitants only (see fig. 6), with increases reaching three times this figure in Spain in 1950 and 1952.

In *Greece*, the number of cases recorded annually between 1931 and 1944 did not exceed 50, according to the official figures. Morbidity since 1947 has been of the same order as in Spain. In 1949 the notification-rate was 4 6 No other outbreak has been observed there since, only a few sporadic cases being notified.

In order to compare, as far as this is permissible, the evolution of poliomyelitis in the various European countries, and to assess the general trend of the disease during the past 30 years, the annual average notification-rates per 100,000 inhabitants have been calculated for each five-year period from 1921 to 1950 and for the period 1951-3. These averages are given in table II. From this table it can be seen that the highest rates are found in the countries of northern Europe, next come Switzerland, Austria,

FIG 6. ANNUAL RATES PER 100,000 POPULATION OF NOTIFIED CASES OF POLIOMYELITIS IN ITALY, SPAIN, AND PORTUGAL, AND OF DEATHS IN ITALY, 1921-53

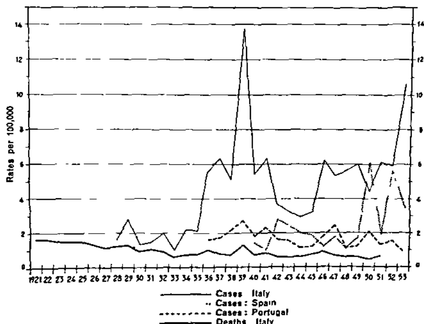


TABLE II. NOTIFIED CASES OF POLIOMYELITIS PER 100,000 POPULATION IN SOME EUROPEAN COUNTRIES (1921-53 *)

Country	1921-5	1926-30	1931-5	1936-40	1941-5	1946-50	1951-3
Austria		1.4	4.2	7.5	4.9	17.1	5.5[a]
Belgium		2.4[b]	1.2	1.0	2.7	1.9	4.6[a]
Bulgaria		0.4[c]	0.7	1.1	3.4	2.2[d]	
Czechoslovakia		0.4[c]	1.6	2.5[e]	5.2[f]	9.8[g]	
Denmark							
all forms	2.8	2.4	30.6	10.7	25.0	16.8	58.9[a]
paralytic				4.9	10.9	4.9	23.5[a]
Finland	1.0	2.7	6.8	8.7	8.1	5.8	4.2[a]
France	0.5[h]	1.1	1.1	1.2	2.2	3.5	3.9[a]
Germany[i]	0.7[h]	2.4	3.2	4.6	4.8[j]	6.2	8.9[a]
Greece			0.3	0.5	0.5[a]	2.1	1.6[a]
Hungary			4.7	5.7	8.0[k]	5.8[l]	
Iceland	248.2[h]	6.7	71.8	26.1	59.0	270.6	28.4
Ireland, Republic of					4.7	5.6	4.6[a]
Italy	1.3[h]	1.5	1.7	7.2	3.9[a]	5.5	7.5[a]
Netherlands	0.3[m]	3.3	1.9	3.1	8.8	2.8	7.5[a]
Norway	6.6	5.3	6.1	9.0	24.4	19.2	38.9[a]
Portugal				2.0	1.5	1.7	1.2[a]
Romania		4.0[c]	0.6	0.8	0.9		
Spain					2.0	2.4	3.7[a]
Sweden							
all forms	5.8	8.0	11.7	23.9	27.2	20.7	28.8
paralytic				20.6	22.8	11.8[n]	17.5
Switzerland	2.7[h]	3.6	4.9	18.4	19.8	14.3	15.5
United Kingdom							
England and Wales	1.5	2.0	1.6	2.4	1.6	11.1	8.9
Northern Ireland	0.3[m]	0.4[o]	1.1[p]	0.6	1.5	8.2	12.6[a]
Scotland	0.6	2.4	1.1	2.2	1.7	11.3	6.8[a]
Yugoslavia			0.5	0.5		0.9	2.0[a]

* 1921-50 five-year averages, 1950-3 average of three years

a Approximate or provisional figure
b 1929-30
c 1927-30
d 1946-9
e Excluding 1939
f Excluding 1942 and 1945
g 1947-9
h 1924-5
i From 1946 Federal Republic
j 1941-3
k 1941-4
l 1946-9
m 1923-5
n Excluding 1947
o 1926-7
p 1933-5

and Germany The morbidity-rates seem to be a little lower in the United Kingdom, Italy, and the Netherlands. The lowest rates have been recorded in Belgium, France, and the southern European countries, with the exception of Italy.

The general tendency for the notification-rates to rise during the period considered clearly emerges from a study of table II. However, the irregularity with which epidemic outbreaks of the disease occur can have varying effects on the five-yearly figures Morbidity is apparently more regular in the populous countries than in smaller ones This is due to the fact that the epidemic outbreaks, which are very variable from year to year, usually occur in territories of a limited area. The national rates in the bigger countries represent the averages of local rates which may be high in certain areas and very low in others However, if, for example, the five-year period 1931-5 is compared with that following the second World War, it can be seen that for most countries the notification-rates have considerably

increased. It is only in Finland that this rate, which was high already in 1931-5, has decreased

Mortality caused by poliomyelitis generally has varied from year to year in the same direction as morbidity. The increase in the number of notifications, and the growing extent of the epidemics, however, have not been accompanied by a corresponding increase in the number of deaths. This fact is shown by table III, where the poliomyelitis death-rates are shown for a certain number of European countries Comparison of tables II and III indicates that the classification of countries in order of increasing mortality is very similar to the classification made on the basis of the notification-rates. Only a few countries show a marked increase in the death-rates, and even in these the notification-rates have increased to a much more marked degree

TABLE III DEATHS FROM POLIOMYELITIS PER 100,000 POPULATION IN SOME EUROPEAN COUNTRIES · FIVE-YEAR AVERAGES 1921-50

Country	1921-5	1926-30	1931-5	1936-40	1941-5	1946-50
Austria		0.2	0.4	0.8	1.0	1.7
Belgium			0.4	0.4	0.5	0.5
Denmark	0.6	0.3	1.0	1.0	1.6	0.7
Finland		0.3	0.6	1.7	1.7	0.9
France					0.7 [a]	0.6
Germany [b]		0.3	0.3	0.4	0.5 [c]	0.8 [d]
Hungary		0.2 [e]	0.6	0.5	0.8 [f]	0.4 [g]
Iceland		2.9	8.0	1.7	1.6	3.1
Ireland, Republic of		0.3	0.2	0.2	1.2	1.0
Italy	1.5	1.1	0.8	0.9	0.6 [h]	0.6
Netherlands	0.3	0.5	0.2	0.3	0.9	0.2
Norway	0.9	0.9	1.0	1.0	4.0	2.4
Portugal				0.2	0.1	0.2
Romania		0.4 [e]	0.3	0.2	0.1	
Spain				0.6 [i]	0.5	0.3
Sweden	1.4	1.1	1.9	2.8	3.1	1.7
Switzerland		0.6	0.8	2.0	2.4	1.4
United Kingdom						
England and Wales	0.4	0.4	0.4	0.4	0.3	1.1
Northern Ireland	*0.4 [j]*	*0.2*			*0.6*	*1.0*
Scotland		0.5	0.3	0.3	0.3	0.9

a 1943-5
b From 1946 Federal Republic
c 1941-3
d 1947-50
e 1927-30
f 1941-4
g 1946-9
h Approximate figure
i 1939-40
j 1923-5

To illustrate these findings more clearly, the case-fatality-rates are shown for the same five-year periods in a separate table (table IV).

Since 1921, from which year onwards sufficiently detailed information is available, the case-fatality-rates have generally decreased The following countries are exceptions to this rule . Austria and Norway, where the case-fatality-rate was relatively high in 1941-5, Finland and Portugal, where the trend is irregular, and finally Germany, where the figures have been of

the same order since 1926 The same table shows that, out of the 20 European countries for which figures are available for the two periods 1941-5 and 1946-50, only two—Belgium and Portugal—have experienced an increase in the case-fatality-rate, whereas it has decreased in the 18 other countries Several factors which may have contributed to this general tendency are discussed later (see page 103)

TABLE IV. CASE-FATALITY-RATES OF POLIOMYELITIS PER 100 NOTIFIED CASES IN SOME EUROPEAN COUNTRIES: FIVE-YEAR AVERAGES 1921-50

Country	1921-5	1926-30	1931-5	1936-40	1941-5	1946-50
Austria		13.2	10 7	11.2[a]	20 1[a]	10 0[a]
Belgium			31 4	39 4	20.8	24 6
Bulgaria		20 7	10 7	10 6	10 0	8.3[b]
Czechoslovakia		38 7[c]	8 7	11.8[i]		
Denmark all forms	20 6	10 8	2 9	9 8	6 6	3.9
Denmark paralytic cases				21.6	15 0	13.4
Finland		10 4[c]	9.3	19.9	21 0	15.9
France					22 7[e]	16 1
Germany[f]		11 7	9 7	9.8		10 7[g]
Greece			9.4	8 7	5 7[a]	4.6[a]
Hungary			13.3	9 4	9.9[h]	6.8[b]
Iceland		42.8	11.2	6.5	2 9	1 1
Ireland, Republic of					26.0	18.5
Italy		76.2	45.2	12.2	16.8[a]	11.4
Netherlands	57 1[i]	14 1	11 9	8 8	10 9	6.6
Norway	13 9	17.6	17 1	11 4	16 4	12.8
Poland		9 8[c]	11 7	9 7[d]		
Portugal				10 8	9 9	14 0
Romania		11.5[c]	47 1	23.5	10 5	
Spain					23 9	12.5
Sweden all forms	24 0	13 9	16 0	11.8	11.4	8 4
Sweden paralytic cases				13 7	13.6	11.8[j]
Switzerland		17 7	17 6	11 0	12.2	10 1
United Kingdom						
England and Wales	25.8	22 4	22 9	16.5	18 1	10.3
Northern Ireland					41 7	12 1
Scotland		21.0	26 4	13.2	16.2	8 4
Yugoslavia		21.0[k]	12 9	13 0		9.5

[a] Approximate or provisional figure
[b] 1946-9
[c] 1927-30
[d] 1936-8
[e] 1943-5
[f] From 1946 Federal Republic
[g] 1947-50
[h] 1941-4
[i] 1923-5
[j] Excluding 1947
[k] 1928-30

Table IV shows considerable differences existing between countries as regards the case-fatality-rate for poliomyelitis The average case-fatality-rates for the period 1946-50 range between 1 1% for Iceland and 24.6% for Belgium. Out of the 22 countries for which such statistics are available for this period, 11 have rates of from 10% to 15%, seven have rates below 10%, and four have rates above 15% For the time being it is impossible to know up to what point differences of such magnitude correspond to variations in the severity of the disease Doubtless, to a considerable extent this disparity should be attributed to appreciable differences between countries, as regards extent and completeness of notification of cases to the health authorities, and the drawing-up of death certificates

increased. It is only in Finland that this rate, which was high already in 1931-5, has decreased.

Mortality caused by poliomyelitis generally has varied from year to year in the same direction as morbidity. The increase in the number of notifications, and the growing extent of the epidemics, however, have not been accompanied by a corresponding increase in the number of deaths This fact is shown by table III, where the poliomyelitis death-rates are shown for a certain number of European countries. Comparison of tables II and III indicates that the classification of countries in order of increasing mortality is very similar to the classification made on the basis of the notification-rates. Only a few countries show a marked increase in the death-rates, and even in these the notification-rates have increased to a much more marked degree.

TABLE III DEATHS FROM POLIOMYELITIS PER 100,000 POPULATION IN SOME EUROPEAN COUNTRIES · FIVE-YEAR AVERAGES 1921-50

Country	1921-5	1926-30	1931-5	1936-40	1941-5	1946-50
Austria		0.2	0.4	0.8	1.0	1.7
Belgium			0.4	0.4	0.5	0.5
Denmark	0.6	0.3	1.0	1.0	1.6	0.7
Finland		0.3	0.6	1.7	1.7	0.9
France					0.7[a]	0.6
Germany[b]		0.3	0.3	0.4	0.5[c]	0.8[d]
Hungary		0.2[e]	0.6	0.5	0.8[f]	0.4[g]
Iceland		2.9	8.0	1.7	1.6	3.1
Ireland, Republic of		0.3	0.2	0.2	1.2	1.0
Italy	1.5	1.1	0.8	0.9	0.6[h]	0.6
Netherlands	0.3	0.5	0.2	0.3	0.9	0.2
Norway	0.9	0.9	1.0	1.0	4.0	2.4
Portugal				0.2	0.1	0.2
Romania		0.4[e]	0.3	0.2	0.1	
Spain				0.6[i]	0.5	0.3
Sweden	1.4	1.1	1.9	2.8	3.1	1.7
Switzerland		0.6	0.8	2.0	2.4	1.4
United Kingdom						
England and Wales	0.4	0.4	0.4	0.4	0.3	1.1
Northern Ireland	0.4[j]	0.2			0.6	1.0
Scotland		0.5	0.3	0.3	0.3	0.9

a 1943-5
b From 1946 Federal Republic
c 1941-3
d 1947-50
e 1927-30
f 1941-4
g 1946-9
h Approximate figure
i 1939-40
j 1923-5

To illustrate these findings more clearly, the case-fatality-rates are shown for the same five-year periods in a separate table (table IV).

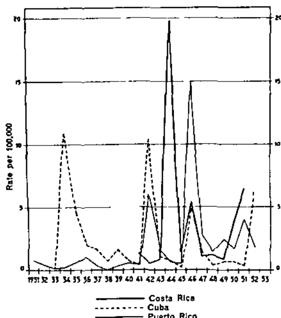
Since 1921, from which year onwards sufficiently detailed information ... The following ... e the case- ... where the ... ve been of

the case-fatality-rate has gradually decreased, during the 10-year periods 1931-9 and 1940-9, it fell to 13% and 7.5% respectively.

In 1952, about 37% of cases were notified as "paralytic" and 22% as "non-paralytic". For the remaining 41% the type was not specified.

In North America, as in Europe, poliomyelitis epidemics show special geographical characteristics, although sporadic cases are usually recorded

FIG. 6. ANNUAL RATES PER 100,000 POPULATION OF NOTIFIED CASES OF POLIOMYELITIS: COSTA RICA, CUBA, AND PUERTO RICO, 1931-52



in each State As a general rule, the local outbreaks are more extensive than in Europe This is not surprising in view of the intense passenger traffic over greater distances than in the Old World Fig 7 shows a striking parallelism between the annual notification-rates in Canada and the USA.

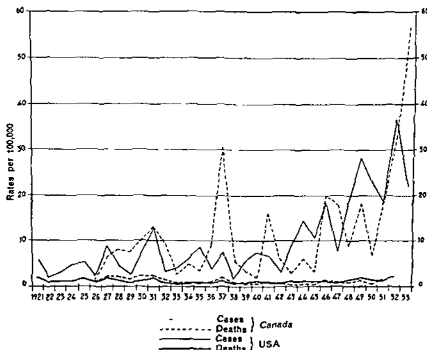
The number of deaths from poliomyelitis varies from year to year in the same manner as the number of cases, however, the mortality-rates have changed relatively little over the past 20 years or so, there being a moderate increase in the USA and a slight decrease in Canada (see fig. 7).

In *Alaska* the number of notifications was high from 1950 to 1953, the rates ranging from 25 to 50 per 100,000 inhabitants.

America

In *Canada* and the *USA*, poliomyelitis is about as prevalent as in northern Europe. The notification-rate has distinctly tended to increase since 1921 (see fig. 7) *Canada* experienced a serious epidemic in 1937, with a rate of 30.6 notifications per 100,000 inhabitants. Serious outbreaks occurred also in 1941, 1946, 1947, and 1949, with rates approaching 20, and another severe epidemic broke out in 1952, with a rate of 33. In 1953 the notification-rate was 56.5 per 100,000 inhabitants, the highest figure recorded up to that year.

FIG. 7. ANNUAL RATES PER 100,000 POPULATION OF NOTIFIED CASES OF, AND DEATHS FROM, POLIOMYELITIS. CANADA AND USA, 1921-53



There were outbreaks of increasing severity in the *USA* in 1944, 1946, 1949-51, and in 1952. In the latter year nearly 58,000 cases of poliomyelitis were notified—a record figure. This number corresponds to a rate of 36.2 cases per 100,000 inhabitants, as against 28.2 in 1949, the maximum rate observed until then. The mortality-rate, estimated on a sample of 10% of deaths, was 2.1 per 100,000 inhabitants; the estimated case-fatality-rate may be put at about 5%. Since 1916, in which year it reached 25%,

The disease is not unknown in *Greenland*, where outbreaks are known to have occurred during the last century in the form of severe epidemics, separated by long intervals.

In comparison with the figures for Canada and the USA, the notification-rates in the Latin American countries appear relatively low. In *Cuba* outbreaks were observed in 1934, 1942, 1946, and 1952 (see fig 8) with notification-rates ranging from five to ten per 100,000 inhabitants, while morbidity in the intervening years corresponded to around one case per 100,000 population

In *Puerto Rico*, epidemics occurred in 1942, 1946, and 1951 (see fig. 8) In *Costa Rica*, there was a severe outbreak in 1944, with nearly 20 cases notified per 100,000 inhabitants.

In *Uruguay*, poliomyelitis was relatively frequent in 1935-7 and 1941-7 (see fig 9) In *Chile* the cases and deaths recorded have increased almost constantly since 1938 (see fig 10). For most other countries on the American continent, information is either non-existent or very incomplete

Table V shows, by five-year period, the average annual rates for cases and deaths officially recorded per 100,000 inhabitants in certain American countries. As in Europe, the usual tendency is for the number of notifications to increase Canada and the USA show an increase in poliomyelitis mortality since 1941-5 For the other countries of the American continent, complete mortality data are not available

Table VI shows the case-fatality-rates per five-year period For Canada and the USA it is evident that these rates have decreased during the period observed In other parts of the American continent a fall in the case-

TABLE V NOTIFIED CASES OF, AND DEATHS FROM, POLIOMYELITIS PER 100,000 POPULATION IN SOME AMERICAN COUNTRIES (1931-53 *)

Notified cases and deaths per 100,000 population in	1931-5	1936-40	1941-5	1946-50	1951-3
Cases					
Alaska		7.5 [a]		13.0 [b]	40.7
Canada	6.4	9.9	6.6	14.2	36.3
Costa Rica	0.7 [c]		4.8	2.4	6.4 [d]
Cuba	5.2 [c]	1.3	2.4	1.5	2.3
Puerto Rico	0.4	0.5 [e]	1.8	4.5	2.5
United States of America	6.9	5.1	8.8	19.2	26.2
Deaths					
Canada	1.1	0.9	0.4	0.8	1.2 [d]
Costa Rica		—	0.8	0.3 [f]	
United States of America	0.7 [c]	0.7	0.8	1.2	1.0 [d] [g]

* 1931-50 five-year averages, 1950-3 average of three years

[a] 1936-8
[b] 1947-50
[c] 1933-5
[d] 1951
[e] 1946-9
[f] Excluding 1948
[g] Provisional figure

FIG. 9. ANNUAL NUMBER OF NOTIFIED CASES OF POLIOMYELITIS IN URUGUAY, 1931-53

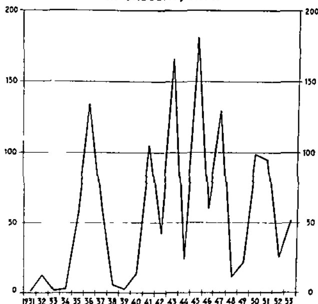


FIG 10. ANNUAL NUMBER OF NOTIFIED CASES OF, AND DEATHS FROM, POLIOMYELITIS IN CHILE, 1932-52

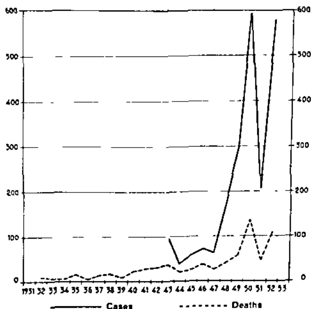
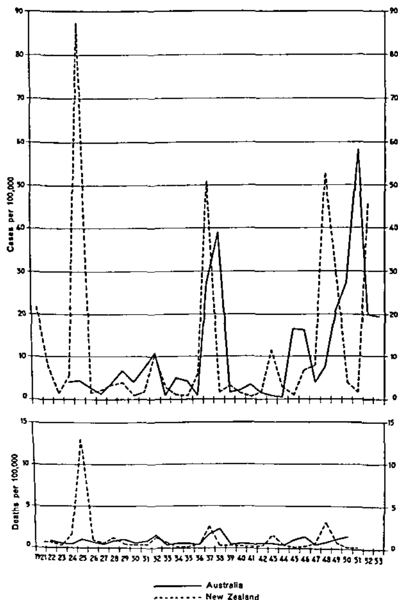


FIG. 11. ANNUAL RATES PER 100,000 POPULATION OF NOTIFIED CASES OF, AND DEATHS FROM, POLIOMYELITIS: AUSTRALIA AND NEW ZEALAND, 1921-53



fatality-rate is also evident, but the figures should be interpreted with great caution.

TABLE VI. DEATHS FROM POLIOMYELITIS PER 100 NOTIFIED CASES IN SOME AMERICAN COUNTRIES: FIVE-YEAR AVERAGES 1931-50

Country	1931-5	1936-40	1941-5	1946-50	1951
Canada	17.8	8.8	5.5	6.0	6.3
Chile	100.0	58.6	59.1	24.5	19.3[a]
Costa Rica			15.6	14.5[b]	
Guatemala			31.2	14.3	6.7[a]
Mexico			100.0	24.5	20.2
Peru			50.6[c]	58.5	
Puerto Rico	20.6	45.9[d]	12.3	8.6	
Trinidad and Tobago	20.0[e]	8.3[d]		22.2	
United States of America	11.5[e]	13.8	8.7	6.4	5.5[f]

[a] 1951-2
[b] 1946-9
[c] 1944-5
[d] Excluding 1938
[e] 1933-5
[f] Provisional figure

Oceania

The incidence of poliomyelitis in *Australia* and *New Zealand* is shown in fig 11. The disease appears to be as highly endemic as in North America, with more marked outbreaks, however, separated by intervals when incidence is lower. *New Zealand* had a notification-rate of 87.3 per 100,000 inhabitants in 1925 , other severe epidemics with rates in the neighbourhood of 50 were observed in 1937, 1948, and 1952. In *Australia*, poliomyelitis developed just as marked an epidemic nature in 1937, 1938, and 1951, with slightly less pronounced outbreaks in 1945-6, 1949-50, and 1952.

A considerable number of cases has also been reported in *Hawaii*, the notification-rate exceeding 10 per 100,000 inhabitants in certain years, and reaching more than 30 in 1952, this corresponding to the figures for the same year in the USA. In the *Gilbert and Ellice Islands*, an epidemic outbreak was observed in 1952

The notification-, mortality- and case-fatality-rates for the principal countries in the geographical area considered are shown in table VII by five-year period since 1921.

Africa

Sporadic cases and localized epidemics have been reported from different parts of the African continent. Apart from data relating to an epidemic in the *Cameroons under French trusteeship* in 1936, with 357 cases notified, all the available figures are of a relatively more recent date. Generally speaking, the number of cases reported in the official statistics is very small, but since all vital and health statistics for this continent are incomplete, it cannot be inferred that poliomyelitis is a rare disease in Africa.

FIG. 11. ANNUAL RATES PER 100,000 POPULATION OF NOTIFIED CASES OF, AND DEATHS FROM, POLIOMYELITIS: AUSTRALIA AND NEW ZEALAND, 1921-53

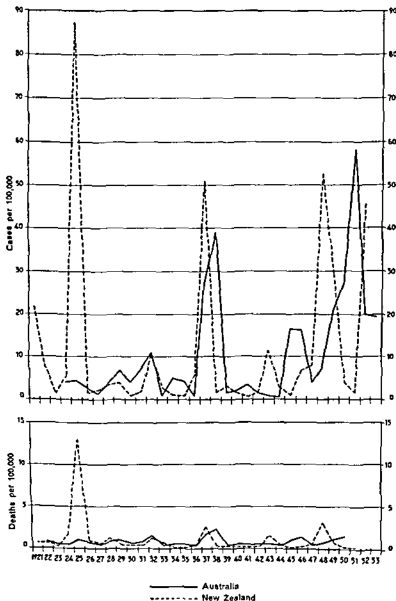


TABLE VII. NOTIFIED CASES OF, AND DEATHS FROM, POLIOMYELITIS PER 100,000 POPULATION, AND CASE-FATALITY-RATE PER 100 NOTIFIED CASES: AUSTRALIA, HAWAII, AND NEW ZEALAND (1921-53 *)

	1921-5	1926-30	1931-5	1936-40	1941-5	1946-50	1951-3
Cases *per* 100,000 population :							
Australia	4.2 *a*	3 7	5 7	14 1	4 6	15 3	32 3 *b*
Hawaii		3 9	2 6	9 0	3 6	4.4	15 8 *b*
New Zealand	25.2	2 4	3 3	12 4	3 5	18.3	23 9 *b, c*
Deaths per 100,000 population :							
Australia	0 7 *d*	0 7	0.7	1.4 *e*	0 5	1 0	
Hawaii		0 4	0 4	1.0	0 2	0 1	
New Zealand	3 4	0 7	0 5	0 7	0 5	0 9	
Deaths *per* 100 *notified* cases :							
Australia	16.8 *a*	18 4	12 4	7.3	11.0	6.3	
Hawaii		9 1	16.3	10 6	4.2	2 6	
New Zealand	13.3	28.5	14 7	5.8	13.3	5 1	

* 1921-50 five-year averages, 1950-3 average of three years

a 1924-5
b Provisional figure
c 1951-2
d 1922-5
e 1936-8

In *Angola* an epidemic broke out at the beginning of 1951, the number of declarations being considerably higher than in any preceding year since 1931 ; the case-fatality-rate reached 8%.

In the *Belgian Congo* the number of declarations has increased since 1945 ; more than 1,000 cases were recorded in 1951, with a case-fatality-rate of 4%

The number of notifications has also been increasing in *Kenya* for some years (see fig. 12).

In proportion to the size of the population, the epidemics which occurred in *Mauritius* in 1945, 1949, and 1952 were exceptionally severe, with notification-rates of 260, 96, and 65 per 100,000 inhabitants respectively.

La Réunion was affected by an epidemic in 1949 ; in *Southern Rhodesia* poliomyelitis endemicity has in general been high in recent years. In the *Union of South Africa* the increase of the disease has been considerable (see fig 12)

Table VIII shows the annual average of poliomyelitis cases notified in [illegible] period Because the

FIG. 12. ANNUAL NUMBER OF NOTIFIED CASES OF POLIOMYELITIS IN BELGIAN CONGO, KENYA, TUNISIA, AND UNION OF SOUTH AFRICA, 1931-53

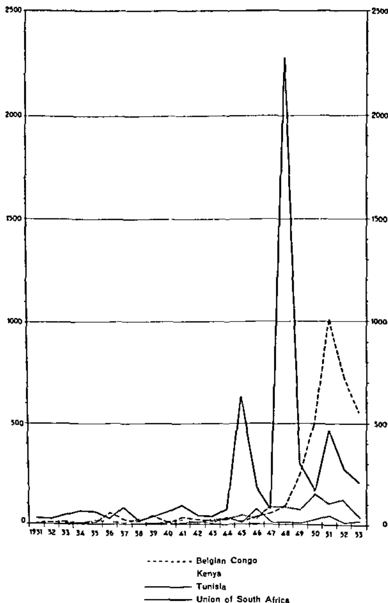


TABLE VIII. AVERAGE ANNUAL NUMBER OF NOTIFIED CASES OF POLIOMYELITIS IN SOME COUNTRIES AND TERRITORIES OF AFRICA (1931-53 *)

Country	1931-5	1936-40	1941-5	1946-50	1951-3
Algeria	6	7	11	32	28
Angola		3	16	11	400[a]
Basutoland		3[b]	5[c]	8	4
Bechuanaland	2	2	1	1[d]	4[e]
Belgian Congo	5	28	21	184	763
Egypt	9	8	9	8	425[e,f]
French Cameroons	*20*[g]	77	1[h]	7	8[e]
French Morocco	3	9	21	20	57[e]
Gold Coast	7	15	10	36	
Kenya	7[i]	9[j]	23	84	90
Madagascar		9[k]	15	124	13
Mauritius			1,103[l]	123	126
Mozambique		4	6	30	30
Nigeria	16	13	19	17[m]	
Northern Rhodesia	1	3[n]	10[o]	13	17
Nyasaland		7	5	12	7[p]
Southern Rhodesia	2	3	12	32	97[e]
Tunisia	2	3	11	23	24[e]
Uganda	3	16	7	26	103
Union of South Africa[q]	44	45	326	601	317[e]

* 1931-50 five-year averages, 1950-3 average of three years

a 1951-2
b 1936-8
c 1943-5
d Excluding 1947
e Provisional figure
f 1953
g 1934-5
h Excluding 1944
i 1933-5
j Excluding 1939
k Excluding 1938
l 1945
m 1946-8
n 1936-8
o 1944-5
p 1951
q From 1931 to 1945, fiscal year ending 30 June, from 1946, calendar year

Asia

Various poliomyelitis outbreaks have been reported from different parts of the Asian continent, but generally detailed information is not available. Table IX gives the annual averages for poliomyelitis notifications, by five-year period, for a certain number of countries only.

TABLE IX. AVERAGE ANNUAL NUMBER OF NOTIFIED CASES OF POLIOMYELITIS FROM ASIAN COUNTRIES (1936-53 *)

Country	1936-40	1941-5	1946-50	1951-3
Ceylon			200[a]	260[b]
Cyprus	2	4	6	4
Iran	425[c]	443		
Iraq	20	24	54	68[d]
Israel (Jewish population)			1,604[e]	810
Japan			2,444[a]	2,902[d]
Jordan				34[d]
Lebanon		2	4	30
Philippines	44[f]		105[g]	78[d]

* 1936-50: five-year averages; 1951-3: average of three years

a 1948-50
b 1951-2
c 1939-40
d Provisional mean
e 1950
f 1936-9
g 1947-50

Epidemic outbreaks of unusual severity have developed in *Israel* since 1950. The number of notifications for this year, namely 1,604, corresponds to 145 cases per 100,000 inhabitants, the case-fatality-rate was 12.6%.

In *Japan*, from 2,000 to 4,000 cases have been reported annually during the past five years. This number corresponds to a rate of 2 5-5 cases per 100,000 inhabitants. However, the case-fatality-rate, which is very high, reaching between 25% and 30%, indicates that in all probability it was mainly the most serious cases which were notified to the health authorities

For other Asian territories, the available information is very fragmentary. A severe outbreak of poliomyelitis occurred at Bangkok in 1952; at Singapore and at Manila incidence has been relatively high in recent years.

Comparison between Notifications of Paralytic and Non-Paralytic Cases

A distinction between paralytic and non-paralytic forms of the disease in the statistical tables is made by only a few countries. For a certain number of them, namely, Denmark, Sweden, Norway, England and Wales, and Canada, the total numbers of cases registered, as well as the percentage of paralytic cases, are shown in table X.

TABLE X. ANNUAL NUMBER OF NOTIFIED CASES OF POLIOMYELITIS AND PERCENTAGE OF PARALYTIC CASES TO ALL CASES FOR CERTAIN COUNTRIES (1948-53)

Year	Denmark		Sweden		Norway		England & Wales		Canada	
	total number	percentage paralytic	total number	percentage paralytic	total number	percentage paralytic	total number	percentage paralytic	total number	percentage paralytic
1948	928	44 0	818	77 8	—	—	—	—	—	—
1949	323	47 4	2,560	72 0	121	91 7	—	—	2,438	47 6
1950	1,571	19 6	1,704	68 3	905	78 0	7,760	71 7	911	31 2
1951	383	5.2	551	61 5	2,233	70 0	2,614	58 5	2,568	44 7
1952	5 676	43.2	492	73 8	715	71 9	3,917	70 1	4 755	45.9
1953	1,591	43 7	5,084	59 6	1,041	82 6	5,250	62 7	8,358	55 7

For Denmark, paralytic and non-paralytic forms have been recorded separately since 1938, and for a still longer period in Sweden. In Norway and Canada, separate notification of the two forms of the disease was introduced in 1949, and in England and Wales in 1950. It can be seen that the proportion of paralytic cases is highest in Norway, being 92% in 1949, a year when incidence was very low, and 70% in 1951, which was an epidemic year. In Sweden, as well as in England and Wales, the ratio of the number of paralytic cases to the total cases notified has varied

TABLE VIII. AVERAGE ANNUAL NUMBER OF NOTIFIED CASES OF POLIOMYELITIS IN SOME COUNTRIES AND TERRITORIES OF AFRICA (1931-53 *)

Country	1931-5	1936-40	1941-5	1946-50	1951-3
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Angola		3	16	11	400[a]
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Belgian Congo	5	28	21	184	763
Egypt	9	8	9	8	425[e,f]
French Cameroons	20[g]	77	1[h]	7	8[e]
French Morocco	3	9	21	20	57[e]
Gold Coast	7	15	10	36	
Kenya	7[i]	9[j]	23	84	90
Madagascar		9[k]	15	124	13
Mauritius			1,103[l]	123	126
Mozambique		4	6	30	30
Nigeria	16	13	19	17[m]	
Northern Rhodesia	1	3[n]	10[o]	13	17
Nyasaland		7	5	12	7[p]
Southern Rhodesia	2	3	12	32	97[e]
Tunisia	2	3	11	23	24[e]
Uganda	3	16	7	26	103
Union of South Africa[q]	44	45	326	601	317[e]

* 1931-50 : five-year averages , 1950-3 average of three years

a 1951-2
b 1936-8
c 1943-5
d Excluding 1947
e Provisional figure
f 1953
g 1934-5
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j Excluding 1939
k Excluding 1938
l 1945
m 1946-8
n 1936-8
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p 1951
q From 1931 to 1945, fiscal year ending 30 June , from 1946, calendar year

Asia

Various poliomyelitis outbreaks have been reported from different parts of the Asian continent, but generally detailed information is not available. Table IX gives the annual averages for poliomyelitis notifications, by five-year period, for a certain number of countries only.

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Cyprus	2	4	6	4
Iran	426[c]	443		
Iraq	20	24	54	68[d]
Israel (Jewish population)			1,604[e]	810
Japan			2,444[a]	2,902[d]
Jordan				34[d]
Lebanon		2	4	30
Philippines	44[f]		105[g]	78[d]

* 1936-50 five-year averages ; 1951-3 · average of three years

a 1948-50
b 1951-2
c 1939-40
d Provisional mean
e 1950
f 1936-9
g 1947-50

TABLE XII. PERCENTAGE DISTRIBUTION OF PARALYTIC AND NON-PARALYTIC CASES OF POLIOMYELITIS BY FOUR-WEEK PERIODS: ENGLAND AND WALES, 1950-3; CANADA, 1951-3

Four-week period	England and Wales, 1950-3		Canada, 1951-3	
	paralytic	non-paralytic	paralytic	non-paralytic
I	3.2	2.0	0.6	0.3
II	2.1	1.5	0.2	0.2
III	2.0	1.3	0.3	0.3
IV	2.1	1.2	0.2	0.2
V	2.1	1.8	0.4	0.4
VI	4.1	3.8	0.5	0.9
VII	9.5	9.8	4.0	3.7
VIII	17.0	20.0	17.2	20.0
IX	18.7	22.9	28.6	31.8
X	14.9	17.7	23.8	26.0
XI	11.6	9.3	13.1	10.5
XII	6.2	5.9	7.6	4.1
XIII	4.5	2.8	3.3	1.6
Total	100.0	100.0	100.0	100.0

is particularly pronounced in epidemic periods and induces the public to consult a physician even in many slight cases which would otherwise go unnoticed. The physician, in turn, will tend to recognize more easily the non-paralytic forms of the disease, whereas the more severe paralytic forms will have almost the same chance of being recognized and notified to the health authorities, whatever the place and season.

Morbidity and Case-Fatality-Rate by Age and Sex

Data on the distribution by age and sex of cases and of deaths are available for only a small number of countries, these, however, are among those where incidence is most pronounced.

For *England and Wales* Logan [20] has analysed deaths from poliomyelitis and cases recorded for the period 1947-50. Table XIII gives the average annual morbidity-, mortality-, and case-fatality-rates by age and sex for this period

It is seen that the notification-rates are higher for males than for females. The distribution of these rates for both sexes over this period is the same: they are highest at 1 and 2 years of age, slightly lower at 3 and 4 years of age, and then decrease for the 5- to 9-years age-group. The rate for children below 1 year slightly exceeds that for the 10- to 14-years group, the rate for the 15- to 24-years group coming next The mean annual death-rate at all ages is 45% higher for males than for females, the death-rate, which is highest in infancy, decreases with age The case-fatality-rate is about 5%

around 2/3. For Canada the ratio was below 1/2 during the years 1949-52; in 1953, when the most serious epidemic ever recorded broke out in the country, the proportion of paralytic cases (56%) was higher than during preceding years. In Denmark, this ratio has varied around 1/3 since 1938; the ratio was only 9% in 1943 and 5% in 1951. These differences from one country to another are considerable; the same applies in each individual country from one year to another. It is not possible to interpret their exact significance. They may be due to differences in the accuracy with which notifications are made, to different ideas as concerns the classification of certain forms of the disease, etc. To assess the importance of these various factors, additional investigations are needed. In any case, such differences require prudence in comparing poliomyelitis morbidity figures.

On analysing the percentage of paralytic and of non-paralytic cases recorded by months or by periods of four weeks, as set out in tables XI and XII, it is found that a relatively high percentage of the notifications made during the seasonal periods of low incidence relate to paralytic forms of the disease.

TABLE XI. PERCENTAGE DISTRIBUTION OF PARALYTIC AND NON-PARALYTIC CASES OF POLIOMYELITIS BY MONTHS: DENMARK, 1941-50; NORWAY, 1949-51, SWEDEN, 1948-52

Month	Denmark, 1941-50		Norway, 1949-51		Sweden, 1948-52	
	paralytic	non-paralytic	paralytic	non-paralytic	paralytic	non-paralytic
January	1.6	0.4	1.5	0.5	4.0	1.2
February	0.8	0.3	0.8	0.3	2.0	1.0
March	0.5	0.2	1.0	0.9	1.6	0.6
April	0.5	0.2	1.0	0.2	0.9	0.4
May	0.9	0.3	1.1	0.1	1.3	0.8
June	1.9	0.8	2.5	1.6	1.4	0.9
July	6.0	4.6	6.0	4.2	3.5	3.6
August	22.6	25.2	10.8	10.5	12.2	14.6
September	33.0	38.4	23.1	28.4	23.1	33.0
October	21.2	19.8	30.8	36.8	26.7	27.7
November	8.1	7.8	14.9	13.7	15.9	12.0
December	2.9	2.0	6.5	2.8	7.4	4.2
Total	100.0	100.0	100.0	100.0	100.0	100.0

In the five countries considered in tables XI and XII, it can be seen that the highest numbers of poliomyelitis cases are recorded around the month of September. The rise in notifications is particularly marked for the non-paralytic forms of the disease.

To account for this apparent concentration of non-paralytic cases in the months of high incidence, it may be supposed that the fear of the disease

For the male sex, the median age was 8.46 in 1944-50, as against 3.93 in 1912-19. For the female sex, the median age rose from 3.90 in 1912-19 to 9.15 in 1944-50 This increase is of a much larger order than any which might arise from changes in the age-structure of the population.

The percentage distribution of cases notified in *Denmark* by age-group since 1911 is shown in table XV This distribution is given separately for paralytic and non-paralytic cases from 1941 onwards.

TABLE XV. PERCENTAGE DISTRIBUTION OF NOTIFIED CASES BY AGE-GROUPS: DENMARK, 1911-53

		0-1 year	1-4 years	5-14 years	15 years and over	Total
1911-20	all cases	8.5	47 1	32 8	11 6	100 0
1921-30	all cases	8.3	37.6	35.0	19 1	100 0
1931-40	all cases	1 8	18.5	47 4	32.3	100 0
1941-50	paralytic cases	4 4	26 9	30.3	38 4	100 0
	non-paralytic cases	2.0	19 0	47 4	31 6	100 0
1951-53	paralytic cases	3 9	34 1	29 6	32 4	100.0
	non-paralytic cases	2 2	24 1	46 6	27 1	100 0

The great majority of poliomyelitis cases observed in the various countries at the beginning of the century were of the paralytic type Thus in Denmark the figures recorded before 1933 referred only to paralytic cases [16] As the disease became better known, a varying number of non-paralytic cases were notified to the health authorities. If, in the course of the years, a change has occurred in the distribution of patients by age-groups, this change must emerge on comparing the percentages for the earliest period (1911-20 in the case of Denmark) with those relating to the most recent periods, neglecting the non-paralytic cases in the latter. Such a comparison shows that

(1) the proportion of patients aged less than 1 year has decreased by half, falling from 8 5 to 4 4 in 1941-50, and to 3 9 in 1951-53 ,

(2) the proportion of patients aged from 1 to 4 years has fallen by about 25%, being 26 9% in 1941-50 and 34 1% in 1951-3, as against 47 1% in 1911-20 ,

(3) the proportion of patients aged from 5 to 14 years has remained more or less stationary, although with a tendency to fall (30 3% in 1941-50 and 29 6% in 1951-3, as against 32 8% in 1911-20) ,

(4) on the contrary, the proportion of patients aged more than 15 years has almost trebled, rising from 11 6% in 1911-20 to 38 4% in 1941-50, and to 32 4% in 1951-3.

TABLE XIII. MEAN ANNUAL NOTIFIED CASES OF, AND DEATHS FROM, POLIOMYELITIS PER 100,000 POPULATION, AND CASE-FATALITY-RATES BY SEX AND AGE: ENGLAND AND WALES, 1947-50

	All ages	Under 1 year	1-2 years	3-4 years	5-9 years	10-14 years	15-24 years	25 years and over
Males								
Notification-rate per 100,000 population	18	32	66	65	49	31	18	4
Death-rate per 100,000 population	1.6	4.0	3.4	3.1	3.0	2.3	2.8	0.9
Case-fatality-rate (percentage of deaths to notifications)	10.4	12.3	5.2	4.8	6.1	7.5	15.2	25.5
Females								
Notification-rate per 100,000 population	12	28	57	53	35	23	14	3
Death-rate per 100,000 population	1.1	3.6	2.7	2.2	2.2	1.6	2.0	0.6
Case-fatality-rate (percentage of deaths to notifications)	9.7	12.7	4.8	4.2	6.1	6.7	14.3	19.3

for both sexes at the age of 1-4 years, slightly higher at 5-14 years, and still higher in the first year of life and at age 15 and over. There is one death for every four cases recorded among male patients aged 25 and above. In most age-groups the case-fatality-rate is slightly higher for the male sex, the rates for all ages being 10.4 for males and 9.7 for females.

It is a well-known fact that the age distribution of notified cases of poliomyelitis during the last decades has changed towards higher ages. Logan has illustrated this tendency in table XIV, where the percentage distribution of notifications by age-group are compared for two periods which are comparatively far apart (1912-19 and 1944-50).

TABLE XIV. PERCENTAGE DISTRIBUTION OF NOTIFIED CASES OF POLIOMYELITIS BY AGE-GROUPS AND MEDIAN AGE OF NOTIFIED CASES: ENGLAND AND WALES, 1912-19 AND 1944-50

		Age-group (years)			All ages	Median age (years)
		0-4	5-14	15 and over		
1912-19	Males	64	28	8	100	3.93
	Females	66	28	6	100	3.90
1944-50	Males	34	37	29	100	8.46
	Females	33	33	34	100	9.15

case-fatality-rates and incidence-rates by age-groups are in an opposite sense to one another (see table XVIII)

This observation applies also to England and Wales, as shown in fig. 13. As concerns Denmark (see fig. 14), only the paralytic cases have been considered in drawing up this graph, but this was not possible for England and Wales, where the distinction between paralytic and non-paralytic forms in the official statistics only dates from 1950.

TABLE XVII CASE-FATALITY-RATES PER 100 NOTIFIED PARALYTIC CASES BY AGE-GROUPS: DENMARK, 1938-52

Year	0-1 year	1-4 years	5-14 years	15 years and over		Total
				male	female	
1938	—	8	11	40	10	14
1939	33	15	20	43	50	29
1940	—	—	20	—	100	20
1941	27	5	18	26	35	17
1942	14	4	14	25	13	13
1943	—	—	17	—	—	7
1944	9	6	10	27	16	15
1945	—	5	8	29	35	20
1946	300	8	8	37	29	28
1947	25	15	5	25	25	17
1948	6	9	18	34	12	15
1949	—	—	3	18	8	6
1950	22	3	7	27	16	12
1951	—	—	20	—	—	5
1952	14	7	8	23	12	11

TABLE XVIII. MEAN NOTIFIED CASES PER 100,000 POPULATION AND CASE-FATALITY-RATES BY AGE-GROUPS: DENMARK, 1947-50

Age-group (years)	Cases notified per 100,000 population		Deaths per 100 cases	
	all cases	paralytic cases	all cases	paralytic cases
0 – 1	35.0	15.3	5.4	12.2
1 – 4	65.0	24.2	2.6	6.9
5 – 14	50.2	10.2	2.0	9.7
15 and over	7.6	2.4	7.0	21.7
Total	19.8	5.7	3.7	12.6

In *Sweden*, poliomyelitis epidemiology has been studied by Olin [23] This author has shown, by comparing the annual average notification-rates by age-groups in 1905, 1911-13, 1925-34, and 1935-44 (see fig. 15), that there is a distinct tendency for the age of maximum incidence of the disease to increase The rates employed refer only to confirmed cases of paralytic poliomyelitis, the years 1905 and 1911-13 were marked by the first extensive epidemics of poliomyelitis in Sweden.

The shift of poliomyelitis in Denmark towards higher age-groups is thus very marked

Table XVI shows the notification-rates for poliomyelitis in Denmark per 100,000 inhabitants as from 1938, from which year onward notifications were made separately for paralytic and non-paralytic forms. For the age-group 15 years and above, these rates are shown for each sex. Generally speaking, since 1945 the non-paralytic cases have been more frequent in each age-group than cases with paralysis. If, for the reasons explained above, only the figures relating to paralytic poliomyelitis are considered, it is found that the rates for the 1- to 4-years age-group are by far the highest. The disease attacks children aged less than one year, and those aged from 5 to 14, almost to the same extent from year to year. As a practically constant rule, male adults are more affected than female adults.

TABLE XVI. AGE-SPECIFIC RATES FOR PARALYTIC AND NON-PARALYTIC CASES OF POLIOMYELITIS PER 100,000 POPULATION: DENMARK, 1938-53

Year	Age-groups (years) for paralytic cases						Age-groups (years) for non-paralytic cases					
	0-1	1-4	5-14	15 and over		total	0-1	1-4	5-14	15 and over		total
				male	female					male	female	
1938	13.8	37.8	18.1	3.2	2.1	7.6	3.1	17.3	28.1	3.1	1.2	7.4
1939	4.6	5.3	1.6	0.5	0.5	1.1	—	3.7	5.6	0.6	0.3	1.5
1940	—	0.8	0.8	0.1	0.1	0.3	—	1.2	0.8	0.2	0.1	0.3
1941	21.4	28.7	18.4	2.4	1.3	8.6	5.7	30.3	31.3	2.5	1.8	8.7
1942	31.0	58.5	38.5	7.9	5.8	15.8	19.7	41.9	62.6	6.1	4.7	17.1
1943	2.6	2.2	2.0	0.2	0.3	0.7	3.8	10.4	22.3	4.4	2.6	6.8
1944	55.6	74.0	45.3	17.6	14.5	25.5	13.1	42.7	69.0	12.1	11.1	22.6
1945	5.5	14.5	8.7	5.2	3.7	5.8	6.7	17.5	39.7	9.0	10.3	14.7
1946	1.1	3.7	1.9	1.3	0.9	1.4	4.3	5.3	9.9	1.8	1.5	2.2
1947	8.5	9.8	3.5	1.6	0.6	2.4	8.5	12.7	26.2	6.3	6.0	9.8
1948	35.3	51.3	14.8	3.8	2.7	9.7	10.3	42.5	34.9	4.1	4.6	12.4
1949	1.2	11.3	8.8	1.8	1.6	3.6	3.7	10.2	11.6	2.0	1.4	4.0
1950	11.6	26.9	13.0	4.1	3.2	7.2	55.3	103.7	85.3	9.6	7.2	29.6
1951	—	1.5	0.7	0.3	0.3	0.5	12.8	16.0	26.1	4.0	3.0	8.4
1952	108.9	288.3	93.5	21.1	26.3	56.5	105.5	305.9	221.7	29.3	31.7	85.2
1953	23.7	59.2	25.0	7.8	5.5	14.0	30.3	68.8	67.5	10.3	8.4	24.0

Table XVII shows the poliomyelitis case-fatality-rates for the same age-groups, for both sexes considered together up to 14 years of age, and for each sex separately above that age. The rates shown have been calculated on the basis of the number of paralytic cases only. This table ... the same facts as table XIII as concerns England and Wales: the

[illegible]

fatality-rate. It is interesting to note that, in general, variations in the

case-fatality-rates and incidence-rates by age-groups are in an opposite sense to one another (see table XVIII)

This observation applies also to England and Wales, as shown in fig. 13. As concerns Denmark (see fig. 14), only the paralytic cases have been considered in drawing up this graph, but this was not possible for England and Wales, where the distinction between paralytic and non-paralytic forms in the official statistics only dates from 1950

TABLE XVII. CASE-FATALITY-RATES PER 100 NOTIFIED PARALYTIC CASES BY AGE-GROUPS: DENMARK, 1938-52

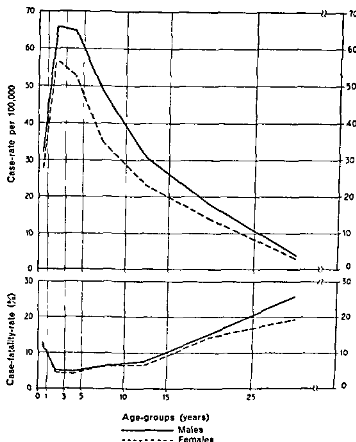
Year	0-1 year	1-4 years	5-14 years	15 years and over		Total
				male	female	
1938	—	8	11	40	10	14
1939	33	15	20	43	50	29
1940	—	—	20	—	100	20
1941	27	5	18	26	35	17
1942	14	4	14	25	13	13
1943	—	—	17	—	—	7
1944	9	6	10	27	16	15
1945	—	5	8	29	35	20
1946	300	8	8	37	23	28
1947	25	15	5	25	25	17
1948	6	9	18	34	12	15
1949	—	—	3	18	8	6
1950	22	3	7	27	16	12
1951	—	—	20	—	—	5
1952	14	7	8	23	12	11

TABLE XVIII. MEAN NOTIFIED CASES PER 100,000 POPULATION AND CASE-FATALITY-RATES BY AGE-GROUPS: DENMARK, 1947-50

Age-group (years)	Cases notified per 100,000 population		Deaths per 100 cases	
	all cases	paralytic cases	all cases	paralytic cases
0-1	35.0	15.3	5.4	12.2
1-4	65.0	24.2	2.6	6.9
5-14	50.2	10.2	2.0	9.7
15 and over	7.8	2.4	7.0	21.7
Total	19.8	5.7	3.7	12.6

In *Sweden*, poliomyelitis epidemiology has been studied by Olin.[23] This author has shown, by comparing the annual average notification-rates by age-groups in 1905, 1911-13, 1925-34, and 1935-44 (see fig 15), that there is a distinct tendency for the age of maximum incidence of the disease to increase. The rates employed refer only to confirmed cases of paralytic poliomyelitis; the years 1905 and 1911-13 were marked by the first extensive epidemics of poliomyelitis in Sweden.

FIG. 13. POLIOMYELITIS CASES PER 100,000 POPULATION, AND CASE-FATALITY-RATE BY SEX AND BY AGE, 1947-50: ENGLAND AND WALES



The distribution of recorded cases by age was almost the same in 1905 and 1911-13, after which the relative proportions of each age-group have changed as follows: they have decreased appreciably for the age-group under 3 years, and to a lesser extent for the 3- to 7-years age-group, but have considerably increased for higher ages (see fig. 15).

The case-fatality-rate in Sweden, as elsewhere, shows increase with increasing age; this has been accentuated between 1905 and 1944.

In 1911-13, the age-group under 3 years had a higher case-fatality-rate than the 3- to 7-years group, the case-fatality-rate increasing above this age; however, during the two periods 1925-34 and 1935-44 the lowest case-fatality-rate was in the age-group under 3 years, increasing thereafter with age (see fig. 16)

Germany

The distribution of notifications by sex and age is not available for all the territory. For Berlin (1946-8), Hesse (1946-7), and Bavaria (1946-8) children aged under 5 had the highest incidence; after this age, incidence decreased with increasing age. Fig 17 gives, expressed as percentages, the distribution by age-group of cases recorded in Berlin for the years 1926-48 The age-shift towards higher ages is unmistakable.

France

For 80% of the 1,665 cases notified in 1952, the distribution by age and sex is known.[15] Table XIX gives the notification and death-rates per 100,000 inhabitants and the case-fatality-rate by age and by sex. It can be seen that the apparent morbidity is higher for the male sex than for the

FIG. 14. CASES OF PARALYTIC POLIOMYELITIS PER 100,000 POPULATION, AND CASE-FATALITY-RATE BY AGE, 1947-50: DENMARK (BOTH SEXES)

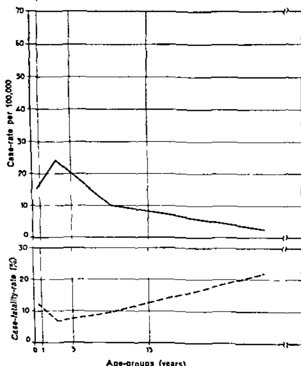
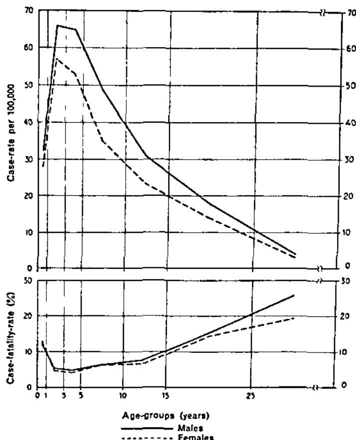


FIG. 13. POLIOMYELITIS CASES PER 100,000 POPULATION, AND CASE-FATALITY-RATE BY SEX AND BY AGE, 1947-50: ENGLAND AND WALES

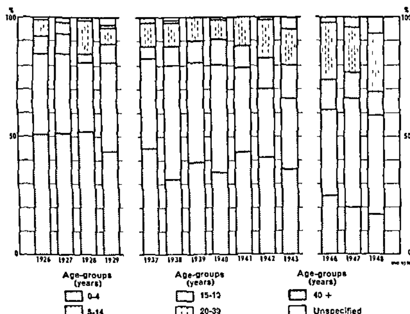


The distribution of recorded cases by age was almost the same in 1905 and 1911-13, after which the relative proportions of each age-group have changed as follows: they have decreased appreciably for the age-group under 3 years, and to a lesser extent for the 3- to 7-years age-group, but have considerably increased for higher ages (see fig. 15).

The case-fatality-rate in Sweden, as elsewhere, shows increase with increasing age; this has been accentuated between 1905 and 1944.

In 1911-13, the age-group under 3 years had a higher case-fatality-rate than the 3- to 7-years group, the case-fatality-rate increasing above this age; however, during the two periods 1925-34 and 1935-44 the lowest case-fatality-rate was in the age-group under 3 years, increasing thereafter with age (see fig. 16).

FIG. 17. PERCENTAGE DISTRIBUTION BY AGE OF NOTIFIED CASES OF POLIOMYELITIS: BERLIN, 1926-48

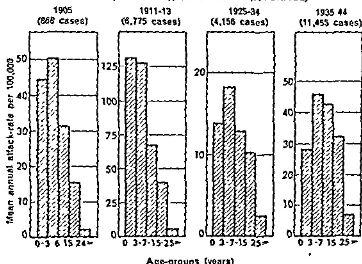


After communication by Dr R S Paine to the Conférence Internationale de la Poliomyélite 17-20 May 1949, by kind permission of the Ligue nationale belge contre la Poliomyélite

TABLE XIX. NOTIFIED CASES AND DEATHS PER 100,000 POPULATION AND CASE-FATALITY-RATES BY SEX AND AGE FRANCE, 1952

Age-group (years)	Cases		Deaths		Deaths per 100 cases	
	male	female	male	female	male	female
Under 1	12.3	6.2	1.4	1.0	11.4	16.1
1 – 4	19.9	16.3	1.2	1.3	6.0	8.0
5 – 9	10.0	7.4	0.7	0.3	7.0	4.1
10 – 14	7.3	3.9	0.5	0.4	6.8	10.3
15 – 19	7.6	5.5	1.4	0.7	18.4	12.7
20 – 24	4.8	3.5	1.1	0.7	22.9	20.0
25 – 29	2.7	2.0	0.9	0.5	33.3	25.0
30 – 34	2.5	1.9	0.9	0.4		
35 – 39	2.1	0.6	1.0	0.2		
40 – 49	0.9	0.4	0.4	0.9	44.3	53.1
50 – 59	0.3	0.2	0.3	0.1		
60 – 69	0.3	0.1	0.1	0.15		
70 – 79	—	—	0.2	—	—	—
80 and over	—	—	—	—	—	—
Total	4.8	3.0	0.7	0.4	14.6	13.3

FIG. 15. CONFIRMED PARALYTIC CASES OF POLIOMYELITIS PER 100,000 POPULATION, BY AGE: SWEDEN 1905, 1911-13 (AVERAGE), 1925-34 (AVERAGE), AND 1935-44 (AVERAGE)



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FIG. 16. CASE-FATALITY-RATE OF CONFIRMED PARALYTIC CASES, BY AGE. SWEDEN, 1905, 1911-13, 1925-34, AND 1935-44

1905 (145 deaths) — 1911-13 (1,239 deaths) — 1925-34 (624 deaths) — 1935-44 (1,594 deaths)

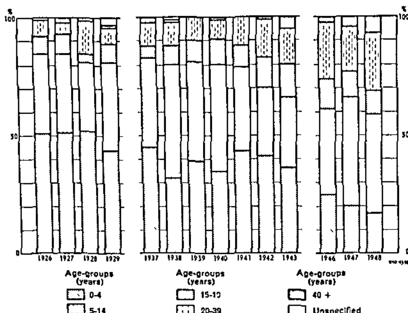
Case-fatality-rate (%)

0 - 3 - 6 - 15 - 24 ➞ — 0 - 3 - 7 - 15 - 25 ➞ — 0 - 3 - 7 - 15 - 25 ➞ — 0 - 3 - 7 - 15 - 25 ➞

Age-groups (years)

Reproduced from Olin[25] by kind permission of Messrs J. B Lippincott Company and the National Foundation for Infantile Paralysis, Inc

FIG. 17. PERCENTAGE DISTRIBUTION BY AGE OF NOTIFIED CASES OF POLIOMYELITIS: BERLIN, 1926-48



After communication by Dr R S Paine to the Conférence Internationale de la Poliomyélite, 17-20 May 1949, by kind permission of the Ligue nationale belge contre la Poliomyélite

TABLE XIX NOTIFIED CASES AND DEATHS PER 100,000 POPULATION AND CASE-FATALITY-RATES BY SEX AND AGE, FRANCE, 1952

Age-group (years)	Cases		Deaths		Deaths per 100 cases	
	male	female	male	female	male	female
Under 1	12.3	6.2	1.4	1.0	11.4	16.1
1 – 4	19.9	16.3	1.2	1.3	6.0	8.0
5 – 9	10.0	7.4	0.7	0.3	7.0	4.1
10 – 14	7.3	3.9	0.5	0.4	6.8	10.3
15 – 19	7.6	5.5	1.4	0.7	18.4	12.7
20 – 24	4.8	3.5	1.1	0.7	22.9	20.0
25 – 29	2.7	2.0	0.9	0.5	33.3	25.0
30 – 34	2.5	1.9	0.9	0.4		
35 – 39	2.1	0.6	1.0	0.2		
40 – 49	0.9	0.4	0.4	0.9	44.3	53.1
50 – 59	0.3	0.2	0.3	0.1		
60 – 69	0.3	0.1	0.1	0.15		
70 – 79	—	—	0.2	—	—	—
80 and over	—	—	—	—	—	—
Total	4.8	3.0	0.7	0.4	14.6	13.3

female sex in every age-group and particularly between 10 and 20 years of age. The maximum morbidity, in both sexes, occurs in the 1- to 4-years age-group. The case-fatality-rate in 1952 was 14.6% for males and 13.3% for females.

Below 5 years, from 10 to 14 years, and above 30 years of age, the case-fatality-rates, however, were higher for females than for males. In the same way as in the countries previously studied, the case-fatality-rate was particularly low for age-groups with a high morbidity-rate (1-9 years); the case-fatality-rate increases thereafter with age.

Fig. 18 shows the incidence by sex and age in 1952.

Spain

The percentage distribution by age of cases registered in Spain in 1952 was as follows: [13]

Age (years)	%
Below 1	28.2
1-2	50.5
3-4	12.7
5-6	3.8
7-8	2.3
9-15	1.5
16 and above	1.0
Total	100.0

Canada

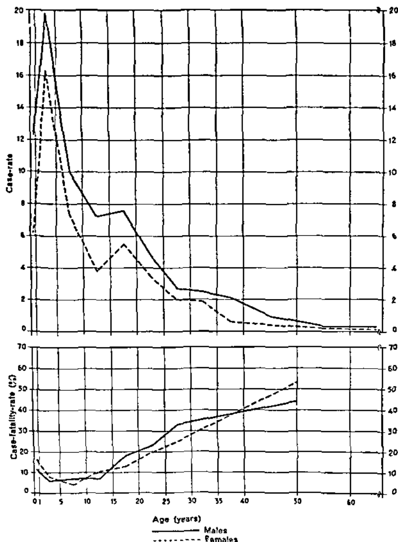
Data for the number of cases of poliomyelitis by age and by sex are available for the year 1952 in six Provinces.

Table XX was compiled on the basis of this documentation. It will be remembered that in 1952 the incidence of poliomyelitis was considerable in Canada. Table XX shows that the highest incidence occurred in the 5- to 14-years age-group, closely followed by the 1- to 4-years age-group. The 15- to 19-years age-group had a notification-rate much higher than

TABLE XX. NOTIFIED CASES OF POLIOMYELITIS PER 100,000 POPULATION BY AGE AND SEX; PARALYTIC FORMS ONLY; SIX PROVINCES OF CANADA, 1952

Age-group (years)	Male	Female	Both sexes
0-1	35.4	34.8	35.6
1-4	78.9	72.2	75.6
5-14	87.3	71.6	79.6
15-19	59.1	59.2	59.1
20 and over	16.4	19.9	18.1
Total	39.6	38.6	39.2

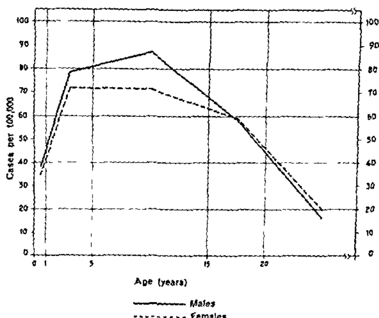
FIG. 18. NOTIFIED CASES OF POLIOMYELITIS PER 100,000 POPULATION, AND CASE-FATALITY-RATE, BY AGE AND SEX: FRANCE, 1952



that for children below one year of age For all groups below the age of 15, the rates for the male sex were distinctly higher than those for females ; in the 15- to 19-years group, both sexes were almost equally affected,

while above 20 years, unlike the usual findings, women were more affected than men (see fig. 19).

FIG. 19. NOTIFIED CASES OF POLIOMYELITIS PER 100,000 POPULATION IN SIX PROVINCES OF CANADA BY AGE AND SEX, 1952



Relationship between Morbidity-Rate and Case-Fatality-Rate

The terms " morbidity-rate " and " case-fatality-rate " are here defined, respectively, as " poliomyelitis notification-rate per 100,000 inhabitants " and " ratio of the number of deaths occurring to the number of cases notified, expressed as a percentage ".

The case-fatality-rate is a very crude measure, since it is influenced by extent and completeness of notification and by completeness of registration of deaths.[19] Other factors influencing this rate are differences in treatment facilities and results, and the time-interval between onset of the disease and death in fatal cases.

There exists between " morbidity-rate " and " case-fatality-rate ", as thus defined, a relationship studied as long ago as 1935 by Biraud & Deutschman[4] in a general study of poliomyelitis. We shall return shortly to the conclusions reached by these authors.

TABLE XXI NOTIFIED CASES OF POLIOMYELITIS PER 100,000 POPULATION, AND CASE-FATALITY-RATES PER 100 NOTIFIED CASES FOR SOME COUNTRIES: 1931-52

Country	Rates	1931	1932	1933	1934	1935	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947	1948	1949	1950	1951	1952
England and Wales	Morbidity	1.0	1.9	2.0	1.7	1.7	1.4	2.1	3.8	2.0	2.6	2.3	1.6	1.1	1.3	2.0	1.6	18.1	4.3	13.7	17.6	5.9	8.9
	Fatality	24.7	23.7	25.3	20.3	20.9	17.7	17.7	16.2	17.2	14.9	16.7	19.6	19.7	20.5	16.2	18.8	9.1	13.0	11.0	9.7	8.3	7.5
Denmark[a]	Morbidity	0.8	2.0	9.8	128.5	10.8	2.1	33.2	7.6	1.1	0.3	6.6	15.8	0.7	25.5	5.8	1.4	2.4	9.7	3.6	7.2	0.5	58.5
	Fatality	13.3	20.5	11.2	2.3	4.5	10.1	10.9	13.9	28.3	20.0	17.2	12.7	7.4	14.8	20.4	27.6	17.2	14.7	5.9	11.7	5.0	10.7
Norway	Morbidity	2.1	3.9	8.3	12.5	3.9	31.9	6.0	3.6	1.9	2.0	60.0	9.4	14.9	13.4	25.2	27.0	21.9	16.1	3.7	27.7	67.7	21.5
	Fatality	24.1	18.9	14.0	16.7	19.6	9.2	17.7	13.3	10.9	25.0	17.6	21.9	16.9	15.3	12.2	15.3	12.4	13.2	9.1	10.9	9.3[b]	
Sweden	Morbidity	1.6	12.6	8.2	18.9	16.8	49.7	30.1	23.0	9.7	7.1	11.3	11.7	33.9	41.4	36.9	8.3	21.8	11.9	36.8	24.3	7.8	6.9
	Fatality	23.5	14.9	16.6	15.2	16.7	13.7	10.9	10.9	9.4	8.9	7.4	10.7	9.6	13.0	12.7	13.3	8.1	10.4	6.4	9.2	8.7[b]	.
Netherlands	Morbidity	1.7	3.0	1.8	2.4	0.8	1.2	0.7	7.9	4.6	1.3	5.0	2.2	21.2	13.3	2.2	3.8	7.2	0.8	1.6	0.8[b]	5.5[b]	16.5[b]
	Fatality	12.5	10.7	14.5	10.2	13.5	16.8	13.3	8.3	6.2	11.7	4.9	10.2	11.5	10.3	22.5	12.0	4.2	3.7	1.2	16.7[b]	6.0[b]	4.3[b]
Italy	Morbidity	1.4	2.0	1.0	2.2	2.1	5.5	6.3	5.1	13.7	5.4	6.3	3.7	3.2[c]	2.9[c]	3.2	6.2	5.3	5.6	6.0	4.4	6.1	5.9[b]
	Fatality	72.4	43.2	62.2	31.8	35.6	18.6	12.3	13.5	9.3	12.0	11.9	18.7	19.3[c]	20.0[c]	21.4	13.6	12.7	10.8	9.6	10.0	9.9	.
Canada[d]	Morbidity	12.9	9.1	2.3	4.8	3.3	8.9	30.6	5.2	3.2	1.7	16.4	5.9	2.8	6.1	3.2	20.6	18.3	9.1	18.6	6.7	18.4	33.0
	Fatality	16.6	17.2	30.0	18.4	17.7	10.0	5.9	14.3	15.6	25.0	3.6	9.3	8.0	5.3	6.2	7.1	3.6	6.3	7.2	4.5	6.3	6.5
USA	Morbidity	12.8	3.1	4.0	5.9	8.5	3.5	7.4	1.3	5.6	7.4	6.8	3.1	9.3	14.3	10.3	18.4	7.6	19.0	28.3	22.0	18.5	37.2
	Fatality	13.2	21.4	15.8	11.3	9.6	17.2	15.4	28.6	10.5	10.5	8.9	13.5	9.2	7.2	8.7	7.2	5.4	6.8	6.6	5.7[b]	5.5[b]	.
Australia	Morbidity	7.2	10.9	0.9	4.9	4.4	0.8	27.2	39.1	1.5	2.0	3.4	1.5	0.9	0.5	16.6	16.3	3.8	7.7	20.8	27.0	56.2	20.1[b]
	Fatality	10.4	13.4	36.2	9.4	12.1	40.4	6.2	5.9	25.0	23.7	10.3	31.8	42.4	55.0	6.2	8.1	7.6	9.3	5.2	5.3	7.3[b]	.
New Zealand	Morbidity	1.7	10.2	2.9	1.0	0.5	5.8	50.8	1.4	3.2	1.4	0.3	1.9	11.6	2.9	0.9	6.8	7.7	53.0	19.6	3.9	1.4	45.8[b]
	Fatality	20.0	12.8	18.6	14.3	12.5	5.7	5.1	18.2	8.2	13.6	50.0	13.3	13.5	11.1	7.1	3.6	6.9	5.7	3.8	2.9	3.8	.

[a] From 1938, paralytic cases only
[b] Provisional figure
[c] Approximate figure
[d] From 1950, including Newfoundland

General trend

Tables IV, VI, and VII indicate the general tendency of the poliomyelitis case-fatality-rate to fall during the past 20 to 30 years. In the course of the same period, the morbidity-rate of the disease, however, has shown an opposite tendency, as has been mentioned in earlier paragraphs.

Cyclic movement

From year to year the morbidity-rate and the case-fatality-rate show considerable variations in the case of a number of countries, as shown in table XXI. When these two series of rates are compared, it is seen that for most of the countries considered, there is a distinct relationship between them, the case-fatality-rate tending to diminish during years of high morbidity but to increase, on the contrary, during years of low morbidity.

Fig 20 shows curves of the rates of morbidity and of case-fatality in Australia, Canada, Italy, and the USA. These curves illustrate the long-term trend for morbidity to increase and the case-fatality-rate to decrease, as well as the opposite nature of the annual variations in these two rates.

Seasonal variations

As with the annual morbidity- and case-fatality-rates, there would seem to be a similar negative relationship between the monthly values of these two rates. For instance, as shown in table XXII, the case-fatality-rate reaches its maximum in those months where morbidity is lowest, and its minimum in the months of high morbidity.

Discussion

"The mere finding of a correlation does not solve a problem. On the contrary it raises one, no longer in the field of statistics but as regards the actual explanation of the phenomena whose existence has thus been demonstrated "[22, a]

Indeed, it must be said that findings similar to those which have been discussed above have been made from time to time in connexion with other infectious diseases. A few years ago, for example, Gover & Jackson[24] reported that in the State of New York, where incidence of cerebrospinal meningitis was high in 1928-9 and 1935-6, but low in the years 1925-6,

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[a] " La constatation d'une corrélation ne résout pas un problème Elle le pose au contraire, non plus sur le plan statistique, mais dans le domaine concret de l'explication des phénomènes dont l'existence est ainsi constatée "[22]

FIG. 20. ANNUAL RATES PER 100,000 POPULATION OF NOTIFIED CASES OF POLIOMYELITIS, AND CASE-FATALITY-RATES: AUSTRALIA, CANADA, ITALY, AND USA, 1931-52

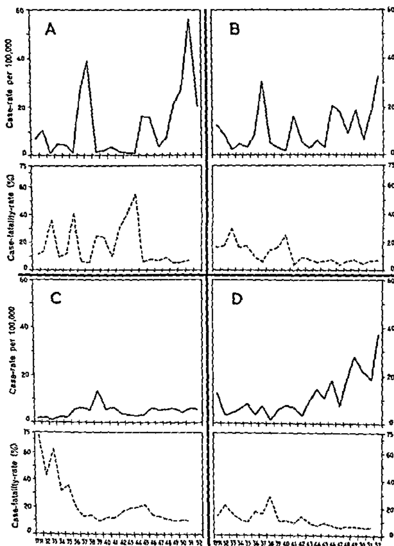


TABLE XXII. PERCENTAGE DISTRIBUTION OF POLIOMYELITIS CASES BY MONTH AND MONTHLY CASE-FATALITY-RATES FOR SOME COUNTRIES

Country and period		January	February	March	April	May	June	July	August	September	October	November	December	Total year
Denmark 1941-50 mean	Cases (%)	1.6	0.8	0.3	0.5	0.9	1.9	6.0	22.8	33.0	21.2	8.1	2.9	100.0
	Fatality-rate	21.5	37.5	52.9	18.8	16.7	5.0	18.9	10.3	13.7	15.4	14.3	29.0	14.5
Sweden 1941-50 mean	Cases (%)	3.0	1.9	1.3	1.0	1.1	1.8	4.7	16.5	26.0	24.7	12.7	5.3	100.0
	Fatality-rate	17.4	18.7	18.0	23.6	11.3	14.9	11.2	7.5	8.2	9.4	10.7	14.6	10.1
Netherlands 1948-52 mean	Cases (%)	0.2	1.0	0.6	1.0	2.3	7.4	17.4	24.1	22.9	14.5	5.9	2.7	100.0
	Fatality-rate	100.0	20.0	33.3	20.0	8.3	10.5	4.5	4.1	2.6	4.1	8.7	14.3	5.2
France 1947-52 mean	Cases (%)	6.9	5.1	4.8	3.1	4.1	6.1	9.4	14.5	15.8	14.2	9.7	6.5	100.0
	Fatality-rate	22.3	32.5	29.5	20.8	26.7	17.3	11.5	12.7	12.4	13.2	15.9	18.1	15.3
USA 1941-50 mean	Cases (%)	1.2	0.8	0.7	0.7	1.3	3.3	11.8	28.0	26.3	16.2	8.2	3.7	100.0
	Fatality-rate	15.3	15.6	16.6	18.0	12.7	9.1	7.2	6.5	5.8	6.9	6.9	8.3	7.1
New Zealand 1947-51 mean	Cases (%)	10.1	7.8	11.4	8.7	9.1	5.5	6.3	6.2	8.3	6.8	7.6	12.4	100.0
	Fatality-rate	6.0	4.4	4.7	4.6	6.7	4.9	3.2	6.5	7.3	4.0	5.3	3.8	5.2

the case-fatality-rate was about 50% during the first two periods but 80% in 1925-6. In connexion with the same disease, one of us wrote :[10]

> " A study of the ' statistical ' case mortality rate of the disease (percentage of notified deaths in relation to number of notified cases) shows ... variations, both cyclical and seasonal, corresponding to the morbidity variations, but in the inverse sense "

In connexion with poliomyelitis, Biraud & Deutschman, in the study mentioned above,[4] bring forward similar facts and suggest the following explanation :

> " All research workers in this field agree that, except during recognized epidemics, it is practically impossible to identify the abortive and aparalytic cases of poliomyelitis ... The conclusions, paradoxical at first sight, resulting from these observations are that the case-fatality rates recorded during a local epidemic are generally lower than those recorded for the whole of a country, and that the lower the rate in a given country, the higher the morbidity (epidemic years), and the higher the rate, the lower the morbidity (inter-epidemic years) "

Such an explanation is no doubt correct. It also accounts, as has been mentioned above, for the apparent concentration of non-paralytic cases during the months of high incidence.

Is it able to account for the progressive decrease in the apparent case-fatality-rate of the disease during the past 30 years ? In part, certainly, for as the number of epidemics increases, the number of " epidemic " cases notified becomes larger and larger as compared with " sporadic " cases, leading to the gradual inclusion of an increasing number of mild forms in the official statistics. Other factors may have tended in the same direction in recent years, for example, certain advances—still very limited—have been made in the treatment of the more serious forms It is doubtful whether the resulting reduction in mortality is of a nature appreciably to affect the case-fatality-rates for poliomyelitis , however, it may have made some small contribution to this. Furthermore, the complaint is better known today than it was at the beginning of the century : there is no doubt that its mild forms are more frequently diagnosed, particularly among adolescents and adults, as the old idea of " infantile paralysis " loses its hold.

To summarize what has been said above, we may accept that there is a negative correlation, which can be explained on grounds of a predominantly psychological nature, between the apparent poliomyelitis case-fatality- and morbidity-rates in the same way as [illegible]

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decrease unduly in "inter-epidemic" periods and to increase in "epidemic" periods, while doubtless remaining always more or less below the number of cases actually occurring. Deaths and serious cases are reported accurately enough; mild cases are notified only when they are numerous.

Conclusions

Poliomyelitis is distinguished from most other notifiable diseases in that only its complicated and exceptional forms ("paralytic poliomyelitis") are reported with any regularity to the health authorities, whereas its usual forms (asymptomatic infection and "non-paralytic poliomyelitis") cannot be regularly notified. In the present study, therefore, much to our regret, no attempt has been made to compare the incidence of poliomyelitic paralysis, which is certainly relatively uncommon, with that of poliomyelitic infection, which is certainly very frequent. Such an enquiry would not be possible on the basis of the data which have been discussed and would call for quite different methods of investigation.

The history of the epidemics which have occurred over the past 30 years or so confirms a known fact, concerning which, however, it is still possible to evolve new theories—namely, that the epidemicity of the disease grows almost from year to year, and that this increasing incidence seems to go everywhere hand in hand with advances in so-called hygiene- and living-standards. Mortality due to poliomyelitis is also increasing, but happily much less rapidly; on the contrary, as has been shown, its apparent case-fatality-rate—i.e., the number of deaths occurring expressed as a percentage of the number of cases notified—shows a negative relationship to the apparent morbidity-rate (notification-rate per 100,000 population, for example). The data at present available are far too fragmentary and inaccurate for the slightest conclusion to be drawn as concerns the probably close and complex relationships doubtless existing between the real incidence and severity of the disease.

Over a long period at least, poliomyelitis has tended to attack subjects of increasingly higher age, and it is known that the highest percentage of deaths occurs among adolescents and young adults. If this trend does not alter, it cannot fail to bring about an increase in the case-fatality-rate of the disease.

Despite their unsatisfactory nature, the morbidity statistics are nevertheless of some value. They are improving, slowly no doubt, but unceasingly. They make it clear that poliomyelitis exists and is extending not only in countries with a "western" civilization, but also in various other countries throughout the world. Wherever this finding is confirmed, more

thorough surveys should be carried out, using other techniques (virological, immunological, etc.) so as to determine the nature of the viruses concerned and the local conditions governing their spread. When the means for the prevention and the control of poliomyelitis which are now being developed become available, such surveys will be necessary before it is possible to decide where, when, and in what way these means should be employed.

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SYMPTOMATOLOGY AND DIAGNOSIS OF POLIOMYELITIS

ROBERT DEBRÉ

Professor of Pediatrics, Faculty of Medicine, University of Paris

STÉPHANE THIEFFRY

Professeur agrégé, Faculty of Medicine, University of Paris
Director, Poliomyelitis Section, Hospital for Sick Children, Paris

THE COMMON FORMS OF INFANTILE PARALYSIS: COMMON SPINAL FORM

Three phases can be distinguished in the development of infantile paralysis:

(1) the incubation phase, occurring between the moment (almost always unknown) of infection and the definite onset of the disease;

(2) the invasion phase (pre-paralytic phase), occurring between the first clinical signs of the disease and the appearance of paralysis; and

(3) the paralytic phase.

Incubation Phase

The average duration of the incubation phase is unknown Ten days is taken to be the commonest figure, but very often it is difficult to do anything more than make an assumption The possibility of prolonged incubation should be recognized a 35-day period has been reported,[10] and a period of more than 40 days noted in a personal observation From the theoretical and prophylactic viewpoint, this gap in our knowledge is a serious one There is no doubt, in fact, that this period during which the virus is present in the infected subject is usually asymptomatic, since the virus has been found in the stools of subjects who showed the first morbid symptoms 12 days[18] or 19 days later.[7] Careful analysis of the anomalies which may occur during this incubation period not infrequently reveals "minor" symptoms, which are without doubt linked with the presence of the virus in the body and represent an initial morbid phase. Such symptoms are fever, sore throat, pharyngitis, nausea, vomiting, abdominal pains, constipation, diarrhoea, and, more rarely, pains or simply abnormal fatigue or a change in temperament This morbid condition, known as the "minor illness", a good analysis of which was

there are pains in the legs, stiffness, and, above all, pains in the back (spine sign). Pain in the lower dorsal region may be of any degree, from simple difficulty in bending to agonizing and excruciating pains which confine the patient to his bed. This pain is experienced in particular when the patient tries to sit down. It is spontaneous, aggravated by changes of posture, and compared by adults to the pain of lumbago. It often spreads towards the buttocks, although rarely reaching the posterior surface of the thighs It is not aggravated by coughing. If it is present, paralytic involvement of the lower limbs is to be feared. On the other hand, when the region affected is high, it is replaced by pain in the neck, sometimes curiously restricted to a few vertebrae, or by pain in the shoulders and upper part of the back. The patient's attitude then sometimes resembles a torticollis

This spontaneous muscular pain sometimes forces the patient to adopt a fixed posture with the shoulders drawn forward, the hips rotated, the arch of the foot hollowed, and the toes pointing downwards The pains may vary in intensity and extent, but they are rarely totally absent and are almost always discovered on careful interrogation. The examination itself, moreover, renders them apparent. They may be so violent that the child fears examination, and in such cases it is best first to collect whatever information can be obtained from simple inspection under the best conditions, namely, in the child's home.

As soon as the examination is begun, the seriousness of the objective pain syndrome can be appreciated. As the patient carries out the movements he is directed to make, he will be able to specify the site of the pains These may be curiously localized, e g, around the shoulder or knee, or may involve a large area of the loins or buttocks On proceeding carefully, it will be seen that there is no paralysis but in fact a limitation of movement due to antalgic reactions as soon as the muscles or muscle groups are stretched This important and very common phenomenon in the clinical study of poliomyelitis is often given the name of "muscular spasm". It is a reflex muscular contraction, independent of the will of the subject, in response to the stretching of the muscle.

The stiffness of the dorsolumbar muscles is one of the most valuable signs of pain in the back. When the subject is asked to sit down, while being held by the shoulders, it is found that he allows his head to fall backwards (which might be wrongly ascribed to paralysis of the anterior muscles of the neck), moving the upper limbs backwards to support himself (tripod sign), and that he cannot hold his trunk upright because of violent pain with spasm of the laterovertebral muscles.

The same phenomenon of painful muscular spasm is frequently encountered in the muscles of the limbs, for instance, when an attempt is made to dorsiflex the foot, to separate the thighs so as to stretch the adductor

recently given by Paul[33] and Russell,[36] does not have a very pronounced clinical individuality, and an etiological diagnosis is the more difficult to make since in this stage no change has yet occurred in the cerebrospinal fluid. This short febrile episode usually occurs within 15 to 20 days before the real clinical onset of poliomyelitis. On the other hand, it may precede it by only a few days. In this case the course of the disease, when it has been possible to follow it in its entirety, has been seen to be a special one. Following an initial febrile outbreak and an initial minor illness, there is a period of apyrexia and apparent recovery; next comes a second attack, coinciding with the onset of the more definite phase of the "major illness", which will be described later under the name of "invasion phase" The designation "diphasic" has been applied to this type of onset, while the accompanying type of temperature curve has been called the "dromedary curve".[16] The abnormal reactions of the cerebrospinal fluid appear only during the second rise in the temperature curve.

Invasion or Pre-Paralytic Phase

Since the first very remarkable description given in 1912 by Peabody, Draper & Dochez,[34] the clinical study of poliomyelitis in the pre-paralytic phase has been given a great deal of attention. The onset is abrupt, occurring at a definite moment, generally at the end of the day, attacking a subject apparently in good health; even if there have been morbid disturbances in the preceding few days, the attack is something new and, from the outset, obviously represents a serious development. In the first few hours the subject complains of headache and almost always vomits. From this time onwards, for a few days, symptoms develop which are specific, distinct, and precise enough to serve as a guide for diagnosis if the signs in this period are familiar or if the physician is on the look-out for them during an epidemic.

Fever is almost always present although seldom very high. It persists throughout the invasion period. The face is almost always flushed, with diffuse reddening of the cheeks and pallor of the peribuccal region. Alternate flushing and pallor of the face is frequent, as are fits of sweating. Phases of mental confusion and somnolence are not exceptional, the patient suddenly recovering from them and replying accurately to questions Symptoms of excitation are much rarer. It is important to note the great rarity of convulsions, even in very young subjects and in the hyperpyretic forms, and even in subjects who have a history of such symptoms.

The patient is restless and complains of pains. Headache persists and pain in the back of the neck is fairly frequent. More often, however,

in various epidemics since that time, sometimes with considerable frequency Wright[47] reported that in the major epidemic in California in 1934, 20% of children and 65% of adults suffered from bladder trouble This trouble is independent of the patient's state of consciousness, and is found particularly in association with later paralytic involvement of the lower limbs. It consists of transitory or lasting retention of urine, necessitating catheterization, or of incontinence which is not always due to retention-overflow The presence of bladder trouble is a strong argument in support of a diagnosis of poliomyelitis Moreover, it is a passing disturbance not found after the first week.

To the essential clinical symptoms, namely, fever, headache, pains, meningeal signs, and sphincter disturbances, must be added symptoms of secondary diagnostic importance Statistics compiled by Grulee & Panos[19] during the Minnesota epidemic give the following frequency for these symptoms vomiting, 50%, diarrhoea, 5%, constipation, 60%; pharyngitis, 55%, sore throat, 20%, and coryza, 10% One or other of these symptoms may predominate in a particular epidemic

Redness of the pharynx and signs of catarrh in the upper respiratory passages are found in about one-third of cases Definite enlargement of the tonsils is more rarely observed

The pre-paralytic invasion phase is variable in length It usually lasts from 3 to 6 days, but it may be shorter, amounting to only 36 or 48 hours, although it is rarely absent It may last as long as 8 days and even, in exceptional cases, 14 days The precise limits of the pre-paralytic phase are clearly easier to determine with older children and adults In common forms of infantile paralysis there does not seem to be any correlation between the intensity of the initial symptoms and the gravity of the subsequent paralysis Moreover, although the nature of the disease may be suspected at this period, it is impossible to be certain that paralysis will inevitably occur and that the attack of poliomyelitis will not be abortive

Acute Paralytic Phase

With the appearance of paralysis a new stage of the disease begins, henceforward of a clearly neurological character

For 4 to 6 weeks following the onset of paralysis many symptoms and signs of the initial acute period persist It is useful to distinguish this stage in practice by naming it the "acute paralytic phase"

The onset of paralysis is usually abrupt, but, as has been seen, takes place after a few days of illness Since the work of West,[45] stress has been laid on the appearance of paralysis as the first clinical symptom, the so-called "morning paralysis" This is exceptional in the case of older

muscles, or to raise the arms to the horizontal, thus elongating the pectoral muscles.

Of all the clinical procedures which can be used to detect this phenomenon, so valuable in reaching an early diagnosis, none is more reliable than Lasègue's sign. This is one of the earliest and most sensitive signs of poliomyelitis, doubtless because raising the whole lower limb above bed-level immediately causes tension in the posterior region of the thigh. In many cases it is sufficient to raise the heel above the bed for a spasm to appear in the hamstring muscles accompanied by a pain which the patient locates in the popliteal hollow. It should be noted that in the initial pre-paralytic phase the pain and tonic reactions to stretching are remarkably symmetrical and are not correlated with the paralyses which appear later on

The objective pain syndrome just described is certainly the most prominent. There is a danger of its masking the meningeal syndrome which may be present at this stage Indeed, it is probable that the symptoms of the two have often been confused. Stiffness of the neck is found in 20% to 30% of cases of infantile paralysis.

Tendon reflexes are rarely changed in the initial period They are almost always normal or lively ; in exceptional cases they may be asymmetrical or may disappear as early as the invasion phase.

The prominence of the pains and the antalgic immobilization may be mistaken for paralysis. In fact, at this period paralysis has not yet appeared However, certain authors have described abnormal movements of certain muscular areas which are on the point of becoming paralysed The terms slight trembling, tremulation, local twitching, shivering, fasciculation, and fibrillation have been used to define such movements Doubtless they are of the same nature as the vermicular movements of muscle in the process of slow neurogenic atrophy When they are present, these localized excitation phenomena are of very short duration.

Abdominal symptoms of poliomyelitis are frequent in the pre-paralytic period In this initial period they may even on occasion become so predominant as to lead to a wrong diagnosis. Abdominal pains are frequent and have sometimes been sufficiently localized in the right iliac fossa to have led to appendectomy.[39] Constipation is the rule, occurring in about 75% of cases. Abdominal meteorism is frequent and peristaltic waves may be observed in the epigastric region.

Bladder disturbances have not been given sufficient attention in descriptions of poliomyelitis. However, urinary disturbances were expressly mentioned by Strumpel[40] as early as 1885 and by Caverly[11] at the time of the 1894 Vermont epidemic (two cases of incontinence and 10 cases of retention out of 132 poliomyelitis cases) They have been observed

All localizations have been observed, since in practice there is no muscle which is immune from poliomyelitis (apart, perhaps, from the plantar flexors). All combinations can be seen: tetraplegia, paraplegia, diplegia, hemiplegia, monoplegia, groups of muscles, a few muscles, one muscle, or a muscle bundle.

Here, for example, is the distribution of paralysis of spinal origin in 229 cases [39]

One lower limb	56
Two lower limbs	40
Upper and lower limbs	48 (including 28 cases of tetraplegia)
One upper limb	22
Two upper limbs	9
Abdominal muscles	32
Back muscles	24

The following general comments may be made

(1) The lower limbs are the ones most frequently affected

(2) Although any muscle may be involved, mention should be made of the very great frequency with which the anterior tibial muscle of the lower limb and the deltoid of the upper limb are affected

(3) Paralysis due to poliomyelitis is usually asymmetrical when two members are affected and very unequal from one muscle to another in the case of a single limb. This asymmetry and patchy distribution is absent only in certain forms of massive paraplegia described under the name of "poliopyramidal form" by Barré [2]

Thus, in the examination of a case of infantile paralysis, it must be described and assessed in terms of the muscle, and not of the spinal root or of the nerve This is the origin of the principle of muscle testing (bilan musculaire)

Moreover, once it has set in, paralysis is generally gross, clearly evident, and easy to recognize, at least in older children and adults. However, it may be difficult, at least during the first days, to arrive at a muscle estimate with any precision, owing to the pain caused.

The paralysis of poliomyelitis is characterized by involvement of the anterior horn and of the peripheral neurones

Tendon reflexes disappear in the area paralysed This occurs at an early stage, as soon as paralysis sets in, sometimes even a little earlier In areas which have apparently been spared, the decrease or disappearance of a tendon reflex may sometimes be detected The abolition of the reflex is generally permanent In a few cases it reappears after a short interval.

Changes in muscle tonus towards hypotonia take place. Actually, this important feature of poliomyelitis paralysis can be demonstrated

children and adults and is found almost exclusively in infants On the contrary, paralysis usually sets in after a period of pains and antalgic immobilization, so that in small children it is difficult to determine the exact moment of onset of paralysis Transitory paresis has sometimes been observed, or even, with subjects who are still ambulant, very short periods of impaired movement Patients who can clearly express their sensations insist, however, on the clear-cut nature of the onset, and many of them can state fairly precisely the way in which paralysis set in and the actual region first affected.

As a general rule, all muscles which will become paralysed are affected in a very short time, either simultaneously or by waves of paralysis at short intervals. It is exceptional for paralysis to take more than three days to become fully developed Stress has been laid on the development of paralysis in two stages, with a fresh attack or new secondary localizations taking place several days or even several weeks after the first attack [38] Experience has shown that such cases are exceptional in genuine spinal poliomyelitis It should also be remembered that certain impairments of muscular function (for instance, of the abdominal muscles) may easily escape notice during a preliminary examination not definitely aimed at finding them, and may subsequently be taken to be new, whereas they had merely not been recognized before.

The onset of paralysis is not concurrent with an alleviation of the general signs or with relief from pain Fever generally persists for a few days longer and sometimes may last for several weeks Subjective pains continue during the first week, and pain caused by examination sometimes becomes even more definite Pain is still caused by movement several weeks or even several months after the onset of paralysis, to such a point that it may be difficult to estimate the state of the muscles correctly Harmful postures and contractions result from the pains.

Usually the meningeal signs die away in a few days, well before the muscular pains

The sphincter disturbances of the initial period rarely persist beyond the first week after the onset of paralysis, unless they are maintained by infection following catheterization. They always disappear without *sequelae. Difficulties of micturition caused by paralysis of the abdominal* muscles should not be mistaken for persistence of the initial sphincter disturbances

In the common form of infantile paralysis described here, the topography of the paralysis is very variable, as capricious as the degree to which the virus spreads over the whole extent of the grey matter, but with a predilection for muscles innervated from the ganglion cells of the lumbar and cervical enlargements of the spinal cord.

Clinical procedures

The strength of a muscle is assessed by studying the maximum displacement it can bring about in the bone segments into which it is inserted, the muscle working under conditions as nearly physiological as possible.

This has given rise to a new technique of clinical investigation, which we cannot go into in detail. On comparing work carried out in various countries, it appears evident that on the whole there is agreement between the methods advocated by the various authors, and consequently a possibility of comparing muscular deficiencies in the same patient in various stages of the disease, as well as of comparing the measurements made by different examiners

With very few exceptions, there is agreement in assigning a conventional "score" to the paralysed muscle, on a scale ranging from 0 to 4 (or 5):

0 = no sign of contraction,
1 = no detectable movement but perceptible contraction of the tendon or of the body of the muscle,
2 = feeble movement, the burden of gravity being eliminated,
3 = movement carried out against gravity,
4 = normal movement against resistance

Now that the necessary modifications have been made, it can be affirmed that the introduction of the muscle-testing technique represents a considerable advance in the clinical study of poliomyelitis Its most important feature is perhaps its extreme simplicity and speed Thus, muscle testing has become a routine examination, since clinical assessment is perhaps more sensitive and certainly more rapid and practical than neuromuscular electrical examination Most workers make use only of the clinical test for arriving at a diagnosis, establishing a prognosis, and taking decisions on treatment

Electrical procedures

(*a*) *Electrodiagnosis by stimulation* makes it possible to study the muscular reaction to a stimulus of either the motor nerve or the body of the muscle Thus the muscles are classified as normal, or as showing reactions of partial or complete degeneration

With these tests should be combined the determination of chronaxy by the method of Bourguignon,[6] or the full excitability curve (threshold intensity as a function of time), as described by British and Scandinavian authors [3 12]

When carried out in the initial period, as early as the second or third day, electrodiagnosis by stimulation frequently reveals qualitative changes in contraction and a considerable increase in chronaxy, sometimes even complete degeneration, a paradoxical fact which raises the question of an

only in the less painful or painless forms, or after a few days, once the initial phenomenon of painful spasm on stretching has died down Search for segmentary hypotonia, for hyperextensibility of the body of the muscle, and for decrease in the resistance of the tendon are excellent methods of detecting paralysed muscles, if symmetrical comparative examinations are carried out

Vasomotor disturbances are almost always found and at a very early stage A change in coloration may occasionally appear very rapidly in very young subjects Careful comparative examination almost always makes it possible to detect localized chilling by simple palpation

Muscular atrophy is a sign to which attention should be paid even in the initial period, since it is possible to detect it very early by systematic measurement and it can sometimes develop with surprising rapidity.

To these positive signs—paralysis, hypotonia, disappearance of reflexes, vasomotor disturbances, and muscular atrophy—must be added equally important negative signs, i e , absence of pyramidal signs, and absence of sensory disturbances These two negative signs call for some qualification Involvement of the pyramidal tract in the acute poliomyelitic process is possible and affords an explanation of exceptional cases of poliomyelitis with transitory exaggeration of the tendon reflexes (seven personal observations) and of less exceptional cases (1% in our personal experience) with a genuine Babinski's sign. The discovery of pyramidal signs is not sufficient by itself for the definite rejection of a diagnosis of infantile paralysis

It is possible to be more categorical as regards sensory disturbances None of the observations reporting or describing such disturbances are beyond nosological criticism Even the most delicate exploratory tests of vibration sense (Buchthal [8]) have been found to give normal results

There is an almost invariable tendency for the paralysis to regress during the acute phase It is, in fact, exceptional not to find at least a limited recovery even in the most severe forms The regression is frequently very distinct and beyond anything hoped for There is no consistency in the time of its appearance; sometimes it commences very early, occasionally even in the first days

Condition at End of First Month

After developing for some weeks, the position becomes clearer and the moment arrives to assess as accurately as possible the extent of muscular deficiency, to attempt a prognosis, and to take decisions regarding specific treatment for each particular case This can be attempted towards the end of the first month

Clinical procedures

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initial peripheral attack on the terminal nerve filaments or, perhaps, on muscle fibre The course of these initial reactions, moreover, is variable.

The traditional time for carrying out an electrical examination to the best advantage is from the 15th day onwards On the whole there is agreement between the clinical and electrical muscle estimates. Thus muscle assigned the score 0 by the clinical methods is found to show partial degeneration.[27]

(*b*) *Electromyography*, which aims at studying differences in physiological *electric potential between two points situated very close together* inside the muscle, has been applied to poliomyelitis [3,6,9,29,37,44]

Although appreciable changes may take place even before the onset of paralysis, the method is of practical interest above all from the 30th day onwards, since it makes it possible ·

(*i*) to observe the phenomenon of fibrillation, which is characteristic of neurogenic muscular atrophy,

(*ii*) to assess the extent to which motor units have disappeared, in accordance with the strength of the curve;

(*iii*) to discover major motor units which are recovering, thus giving hope of functional compensation.

Prognostic Factors

The patient who has just passed through the acute phase of the disease *remains afflicted with more or less serious physical disability. After several* weeks, a month on the average, the paralysed patient enters a new period of the disease, which is often given the name of chronic phase, or phase of sequelae

In reality, poliomyelitis during what is termed the chronic phase may still undergo changes in the direction either of improvement or of complications. The final stage, that of the true sequelae, is only reached after at least two years—very often much longer. Multiple factors are involved *during this restitution period and it is extremely difficult to determine the* one which dominates Indeed, each case must be considered on its own.

The following factors are involved. nerve regeneration, i e., the possibility of a damaged nerve cell resuming its functions; the topography of the paralysis, which in many cases leads to secondary deformations; so-called trophic disturbances which go far beyond the muscular system; the effect of treatment, immobilization in bed, and over-stretching of muscles in the case of subjects with severe paralysis; physiological adapta*tion to the disability* by the setting-up of new reflex systems Finally, psychological and social factors must also be considered.

An experienced clinician, however, will succeed in arriving at a prognosis with a very large degree of certainty The admirable study by Lassen,[26] concerning the long-term prognosis of infantile paralysis, may be quoted as an example This author was careful to carry out systematic examinations, over a period of three years and longer, of poliomyelitis patients whom he was able to examine from the acute period onwards.

From this study, and the qualified findings of the author, the following conclusions can be drawn

(1) It is doubtful whether a muscle which has been completely paralysed after an attack of poliomyelitis (score 0) can become completely normal again (1 4% are exceptions to this rule)

(2) Muscles which have been severely but not completely paralysed (score 1 or 2) at the end of the acute period (about 20%) become normal again, and more than 50% regain functional value

(3) In cases where muscles have been slightly paralysed or have shown a decrease in strength only (score 3), chances of complete recovery are 90%

(4) However, about one-eighth (12 5%) of partially paralysed muscles do not recover, and only in 50% of cases does progress continue after a year

(5) Three-quarters of complete functional recoveries take place in the first year, somewhat less than one-quarter during the second year, and less than one-twentieth during the third year

It should be added that chances of recovery vary according to the muscle involved The muscles of the back, the lumbricales of the foot, the opponens pollicis, and the abdominal muscles are those which have the least chance of recovery

The Chronic Phase

Thus, in the chronic phase, a variable degree of disability must be expected, with muscle deficiency differing greatly from one patient to another In addition to this, the position of the patient and his functional difficulties may be aggravated by a series of complications

Atrophy of the paralysed muscle is a direct consequence of muscular inactivity It is largely overcome or decreased by physiotherapy However, certain forms of atrophy develop at a remarkably early stage and proceed inexorably for physio-pathological reasons as yet undefined

Deformities threaten all patients with severe muscular deficiency. They are linked, above all, with the action of gravity and with immobility, and are aggravated and fixed by muscular, tendon, and capsulo-ligamentary contractions

The trophic disturbances associated with poliomyelitis are of capital importance. The most serious involves bone-growth, as reported by Heine [21] in his original paper in 1840 Shortening of the paralysed limb is to be feared, above all in young children, in the event of extensive and severe paralysis, with vascular disturbances and considerable coldness, and also, according to Nathan,[29] in the event of paralysis of the posterior muscles

The skin is also often affected, becoming smooth, atrophic, less elastic, discoloured, pigmented, or pink The patient suffers from cold feet. Local œdema is not uncommon. Perspiration is increased. The response to cooling and warming is altered. Certain subjects suffer from very painful cramps when they try to "force" muscular activity.

Finally, it should be remembered that with severe cases of paralysis obliged to remain in bed there may be calcium precipitation with renal calculus formation, associated with osteoporosis Death from renal insufficiency is not exceptional.

To summarize morbidity due to ordinary infantile paralysis is negligible (1%); motor sequelae are the rule. it can be estimated that at present 7% of patients remain incapacitated for work, while 75% are left with their working capacity reduced

Positive Diagnosis: Routine Laboratory Tests

The blood picture is usually normal Leukopenia is sometimes found in the initial phase Consequently this examination is of little value for clinical diagnosis

Chemical changes in the blood are also of little practical interest There is progressive hypoproteinemia up to the tenth day and hypopotassemia in the severe paralytic forms

On the other hand, changes in the cerebrospinal fluid are sufficiently constant and characteristic to constitute one of the best aids to diagnosis.

Since the initial discovery by Draper & Peabody [16] in 1912, the general studies of Neal & Abramson,[30] Kolmer et al,[22] Rohmer et al,[35] and of Thieffry,[41] have demonstrated the extreme frequency with which a meningeal reaction occurs in the spinal fluid, and established the trend of cytological and chemical changes in the disease In our own experience, although cytological and chemical changes in the spinal fluid may occur separately, they are almost always associated with one another (99% of cases). They thus constitute a biological test of considerable value to the physician

Pleocytosis is the rule in the acute period It reaches a maximum during the first two days of the disease, but a cell count of 400 is rarely

exceeded. It rapidly decreases from the third day, but persists to a reduced extent during the second week of the disease.

The cells found in the spinal fluid change in the course of paralytic poliomyelitis The initial polynucleosis is transitory and disappears in two or three days; it is replaced by a reaction in which large and small lymphocytes predominate Histiocytes are present in the spinal fluid during the first two weeks of the disease

The change in the protein content of the fluid follows a special course. It is high during the first week, like the cell count, decreasing towards the tenth day, but increasing again in a secondary stage (1 g and up to 4 g per litre). Thus there is albumino-cytological dissociation during the third and fourth weeks, and sometimes even in the second week.

Differential Diagnosis of Paralytic Poliomyelitis

The diagnosis of infantile paralysis is not an obvious one The proportion of diagnostic errors is close to 15%

Foremost among the group of non-neurological complaints which may be mistaken for poliomyelitis are the articular or osteoarticular diseases Diagnoses of acute articular rheumatism are fairly often wrongly made in the invasion phase, and, conversely, genuine cases of rheumatism are sometimes mistaken for infantile paralysis The same error is sometimes made with osteomyelitis Experience has shown that acute forms of arthritis in children represent the most frequent cause of confusion The difficulty is greatest with infants This is understandable in view of the mildness of the general signs and the difficulty of delineating the area affected by paralysis in cases of poliomyelitis in early life Common pyogenic infective arthritis, syphilitic osteoarthritis, and scorbutic osteosis are included under the heading of infantile "pseudoparalysis"

All the mistakes mentioned above are sometimes rectified at a late stage, an accurate diagnosis being reached only retrospectively Many such errors are avoidable if caution is shown before accepting a diagnosis which may at first sight be thought obvious

It is above all in the diseases of the nervous system that the greatest difficulties are encountered However, it is essential clearly to differentiate poliomyelitis from other affections which may resemble it in certain clinical characteristics, and not to increase the range of clinical symptoms of poliomyelitis without unmistakable anatomical or etiological proof.

When the findings do not fit into the usual clinical picture and one or more anomalies are discovered, a diagnosis of poliomyelitis should not be made without reservation, and it may have to be rejected suddenly.

There is every likelihood that the illness concerned is really another disease of the nervous system or possibly a muscle complaint concerning whose poliomyelitic nature there is still some doubt. We discuss below examples from various fields of nervous pathology.

(1) Among diseases of the spinal cord, traumatic haematomyelia and acute paralytic attacks of syringomyelia warrant no more than a mention. On the other hand, during the first days there may be a very pronounced resemblance between acute myelitis and acute anterior poliomyelitis However, clinical differentiation should be easy when the pyramidal signs, sphincter disturbances, and sensory disturbances become definite as the disease progresses The same fundamental remarks may be made concerning meningoradiculomyelitis, whether this is primary or secondary to an infectious disease

(2) The largest number of diseases which most closely resemble poliomyelitis are found among affections of the spinal roots and the peripheral nerves "Polyneuritis" should give rise to little difficulty, in view of the circumstances attending its appearance and the peculiar features in its development Thus, the constancy of paralysis of the soft palate, the frequency of ocular involvement, and the disturbances of deep sensation in paraplegic cases are sufficient to suggest diphtheria; the nervous symptoms in botulism are accompanied by digestive symptoms; the forms of polyneuritis produced by arsenic, lead, apiol, and triorthocresylphosphate are easily distinguished, if only by their gradual development, their habitual symmetry, the occasional presence of sensory disturbances, and the absence of change in the cerebrospinal fluid

On the other hand, matters are quite different for the radiculoneuritis group Here the spinal roots and nerves constitute the site of the lesion, the motor cells of the anterior horn not being involved This results in motor and possibly sensory symptoms, reminiscent of those of poliomyelitis The majority of such cases of polyradiculoneuritis (PRN) are accompanied by a special change in the spinal fluid, in the form of albuminocytological dissociation. The course of the disease is usually favourable, and recovery without sequelae can be counted upon PRN should be classified as a definite morbid entity and given the name of Guillain-Barré's syndrome or disease. These two authors (together with Strohl [20]) drew attention to this complaint in 1916 and described in a definitive manner a disease in which motor and sensory paralysis is accompanied by albuminocytological dissociation in the spinal fluid, recovery taking place without sequelae. All subsequent work has served to confirm the existence and frequency of Guillain-Barré's syndrome in adults and children.

We are still without any idea of the etiology of this morbid entity, but it may be affirmed that at the present time there is no argument, either

clinical, anatomical, or biological, justifying classification of this disease under poliomyelitis. Consequently, it is very important to distinguish these two complaints ; unfortunately, they are still regularly confused with one another.

Thus, to give an example, the statistics collected by Debre & Thieffry[14 15] in the Poliomyelitis Section of the Paris Hospital for Sick Children show the frequency of the disease and reveal errors in diagnosis. In the course of three years, 438 poliomyelitis cases were admitted to this hospital clinic, as well as 36 cases of radiculoneuritis of the Guillain-Barré type (about one case of PRN to 12 of poliomyelitis) Among the 36 cases of Guillain-Barre's syndrome, an accurate diagnosis before admission had been reached on only one occasion.

Nevertheless, there are differences between the two complaints which are easily discovered on interrogation, clinical examination, and study of the cerebrospinal fluid, and which usually make differential diagnosis simple and rapid. These differences can be summarized as follows

(*a*) The invasion period, which is constant and febrile in poliomyelitis, is absent in PRN in half the cases, when the disease commences straightaway with paralysis, without any premonitory symptoms, invasion phase, or fever

(*b*) The onset of paralysis, which is usually sudden or abrupt in poliomyelitis, is sometimes more gradual in PRN

(*c*) The phase during which paralysis spreads is usually short in poliomyelitis, in which, in practice, there is no danger of further muscle involvement after three days, in PRN, on the contrary, new areas are very often attacked in successive stages a few days apart, it being possible for the period of extension to spread over several weeks.

(*d*) The topography of the paralysis is very different in both cases Poliomyelitic paralysis is usually distributed capriciously without any particular order and in an asymmetrical manner. On the contrary, in PRN paralysis generally spreads to a whole limb or to a proximal or distal segment of the limb, the bilaterality and symmetry of the motor involvement being very remarkable

(*e*) In the initial period poliomyelitis makes a massive attack on the motor functions, moreover, the different muscles are usually affected to a varying extent In PRN the attack is much more often relatively limited, being more of the nature of pronounced paresis than actual paralysis, and is equally distributed over all the muscles in the region affected

(*f*) Reflexes are electively abolished in the paralysed region in the case of poliomyelitis In PRN, on the contrary, there is usually a

diffuse abolition of all tendon reflexes, even in areas which have apparently escaped.

(*g*) Spontaneous pains are perhaps more acute in poliomyelitis, while PRN is characterized by paraesthesiae of the extremities (an exceptional phenomenon in poliomyelitis) In children it is not uncommon to observe some local and general symptoms reminiscent of aerodynia.

(*h*) The sensory changes absent in poliomyelitis are seen with some frequency in Guillain-Barré's syndrome.

(*i*) Study of the cerebrospinal fluid supplies a conclusive argument in differential diagnosis. A diagnosis of Guillain-Barré's syndrome is confirmed by the finding of pure albumino-cytological dissociation without any change in the cell count. Recent systematic research makes it clear that hyperalbuminosis appears at an early stage, is evident from the fourth day following the clinical onset, reaches its maximum intensity towards the seventh day, and still remains evident for several weeks This shows the importance of lumbar puncture for examination of the spinal fluid at the commencement of the disease, i e , at a time when the problems of diagnosis and prognosis are most difficult and most important.

(*j*) The course of the two diseases is fundamentally different In poliomyelitis, as is well-known, paralytic sequelae are to be feared, on the other hand, a favourable prognosis is, on the whole, justifiable in the case of Guillain-Barre's syndrome, since regression, followed by complete recovery without sequelae, may be anticipated, although certain authors mention an unfavourable course and fatal accidents It would seem that a certain number of these could be avoided by paying special attention in examination and treatment to paralysis of the respiratory muscles and difficulties in swallowing

(3) Some affections of the central nervous system may be more or less legitimately confused with poliomyelitis It should be remembered that, at present, the possibility of the poliomyelitis virus producing sufficiently extensive lesions in the cortex to bring about corresponding clinical symptoms is not supported by any valid argument. In particular, the observations frequently cited of hemiplegia caused by cerebral lesion during poliomyelitis call for serious criticism.

Errors may arise in exceptional cases due to confusion with paralytic chorea, acute neuromyelitis optica, and familial periodic paralysis. Acute ataxia is more frequent and is sometimes confused with poliomyelitis in children. It has been studied by one of us (Thieffry et al.[43]), and a morbid entity of frequent occurrence in children—namely, curable acute cerebellar ataxia—has been differentiated This is a disease in which the onset is abrupt and where difficulty in walking and standing is linked with cerebellar

disturbances, without any decrease in muscular strength. Acute cerebellar ataxia, such as we have tried to define, cannot be in any way linked with poliomyelitis and, in particular, is absolutely different from certain types of poliomyelitis reported by Wickmann[46] with initial transitory signs of ataxia, which are sometimes found together with the other usual paralytic symptoms of poliomyelitis

(4) In the field of muscular pathology it has been reported that dermatomyositis might be confused with polyneuritis or the initial phase of poliomyelitis This calls for no more than a passing mention.

The problem of epidemic myalgia or Bornholm disease calls for closer attention It has been suggested on several occasions that this disease is of poliomyelitic origin In fact the clinical picture, dominated by violent muscle pains—predominantly thoracic (epidemic pleurodynia)—hardening of the muscular masses, and sometimes meningeal reaction, differs fundamentally from that of poliomyelitis Paralysis is unknown in Bornholm disease From the epidemiological viewpoint, there is no connexion between the two complaints From the viewpoint of virology it has been agreed that the idea of the poliomyelitis virus playing a part in Bornholm disease should be rejected Particular attention is being paid to the Coxsackie group of viruses,[13, 17] although in our opinion any definite conclusion would be premature at this stage

SPINAL FORMS WITH PARALYSIS OF THE RESPIRATORY MUSCLES

Among the spinal forms of poliomyelitis, a special place must be reserved for those accompanied by paralysis of the respiratory muscles. Such forms follow attack by the pathogenic virus on the centres governing the main and accessory respiratory muscles and situated in the spinal cord (from about C3 to D12) The name "paralysis of execution" may be given to this type of paralysis as opposed to "paralysis of respiratory command", which will be studied in connexion with the bulbar forms of the disease

A systematic study of the respiratory function should be made in the case of every patient suffering from poliomyelitis, whatever the extent of the paralysis and despite good respiratory behaviour. If the examination reveals any impairment of the respiratory function, special surveillance is essential

Paralysis of the respiratory muscles usually accompanies serious cases of poliomyelitis, affecting all four limbs and the trunk It may, however, also occur in apparently mild or slight poliomyelitis, where only a few shoulder or neck muscles are paralysed

The functional signs, when they exist, take the form of polypnea. This may be hardly noticeable. Coughing becomes weakened or impossible. The voice is also weakened and the ability to talk impaired (as can be shown by making the patient count during exhalation). The respiratory rhythm remains unchanged and the patient retains the ability to alter it at will or to stop breathing This is a sign of great value when its presence can be definitely ascertained, but the age or mental condition of the subject often makes interpretation a delicate matter.

Simple clinical examination usually makes it possible to recognize and define respiratory paralysis, provided that attention is paid to the three muscle groups of respiration, i.e , the intercostal, diaphragm, and abdominal muscles

The intercostal muscles are mainly concerned with inspiration. Their action enlarges the thorax by lifting and separating the ribs and thrusting the sternum forward. In the paralysed state, enlargement of the thorax is no longer found on inspiration, as can be detected by palpation and measurement (carried out, if necessary, at several different levels and on each side of the thorax) A paradoxical enlargement of the thorax can, however, take place during expiration In quiet respiration there is a descending movement of the thorax towards the abdomen One of the best signs, although an indirect one, of deficiency of the intercostal muscles, is the vicarious action of the accessory inspiratory muscles, which appears spontaneously when the patient is tired or when he is asked to inhale as deeply as possible This results in suprasternal depression, and contraction of the sterno-mastoid muscles, the scalenes, as well as, sometimes, the pectoral and dorsal muscles

The most frequent form is paralysis of the diaphragm Bilateral paralysis results in the appearance of distinctive signs . simultaneous lifting of the thorax and abdomen during inspiration is replaced by a see-saw thoraco-abdominal movement, caused by inspiratory depression of the epigastrium It is more difficult to be certain concerning unilateral paralysis. It will be found a good plan to compare the behaviour of the lower intercostal spaces on deep inspiration Fluoroscopic examination is particularly useful here for studying the mobility of the two halves of the diaphragm The presence of paralysis of the muscles of the abdominal wall makes clinical interpretation difficult

The abdominal muscles must be considered here as respiratory muscles. They play a very important role in helping the diaphragm to press the abdominal mass before it , furthermore they are of great importance in forced expiration and the mechanism of coughing Abnormal umbilical movements during the effort of coughing afford an early sign—an excellent and easily detectable one—of the involvement of these muscles.

In determining the degree to which the respiratory muscles are paralysed, the usual procedures of percussion and auscultation should not be neglected Whenever possible, fluoroscopy or radiographs taken during the two stages of respiration give valuable information, e g , by confirming anomalies in the position of the ribs or collar bone, showing up diaphragmatic paralysis, or revealing opaque areas, whether associated or not with organic displacement, caused by total or lobar atelectasis.

On the whole, the prognosis of respiratory paralysis is grave.

Paralysis affecting, for example, the upper intercostal muscles or one side of the diaphragm may not lead to immediate or rapid functional disturbances. Similarly, extensive paralysis of the abdominal muscles may subsequently, but at a late stage, have an effect on respiration There may even be such a long interval between the acute phase and the first apparent respiratory symptoms that the connexion is not seen, although it is indisputable and readily explicable (disturbances of ventilation, infection), if the frequency and the importance of the sequelae of respiratory paralysis are not clearly realized

As soon as a patient is deprived of the use of a large proportion of the respiratory muscles and, above all, if he can no longer depend on the diaphragm, the position becomes more serious and a development towards asphyxia will soon follow The subject will resist for a few days and finally succumb to pulmonary obstruction and hyperthermia

In such circumstances the course of events is completely dependent on the aid which can be given by artificial respiration, the technical facilities available, and the quality of the care which can be given to the patient There is no doubt that technical advances and the experience acquired during the past ten years have greatly modified the prognosis of respiratory paralysis Although mortality in the first days is still fairly high in the massive forms of paralysis (above all in the case of bulbo-spinal poliomyelitis), nevertheless a certain number of survivals have been recorded with respiratory sequelae and even cases of recovery Laruelle & Schwartz[25] believe that a patient transferred to an iron lung has a 36% chance of survival, and the survivors have one chance in two of returning to a normal existence

Such results, which were unhoped for a few years ago (mortality was close to 90% in 1940), are due to a better prevention of mechanical accidents (atelectasis) and of the infectious accidents which are so often associated with respiratory paralysis Total recovery of the respiratory muscles, although possible, is rare, and stress should be laid on two essential points concerning the future of these patients on the one hand, the considerable difficulty represented by any persistent respiratory insufficiency in motor re-education and, on the other, the frequency of respiratory sequelae.

The functional signs, when they exist, take the form of polypnea. This may be hardly noticeable Coughing becomes weakened or impossible The voice is also weakened and the ability to talk impaired (as can be shown by making the patient count during exhalation). The respiratory rhythm remains unchanged and the patient retains the ability to alter it at will or to stop breathing This is a sign of great value when its presence can be definitely ascertained, but the age or mental condition of the subject often makes interpretation a delicate matter.

Simple clinical examination usually makes it possible to recognize and define respiratory paralysis, provided that attention is paid to the three muscle groups of respiration, i.e , the intercostal, diaphragm, and abdominal muscles

The intercostal muscles are mainly concerned with inspiration. Their action enlarges the thorax by lifting and separating the ribs and thrusting the sternum forward. In the paralysed state, enlargement of the thorax is no longer found on inspiration, as can be detected by palpation and measurement (carried out, if necessary, at several different levels and on each side of the thorax) A paradoxical enlargement of the thorax can, however, take place during expiration In quiet respiration there is a descending movement of the thorax towards the abdomen One of the best signs, although an indirect one, of deficiency of the intercostal muscles, is the vicarious action of the accessory inspiratory muscles, which appears spontaneously when the patient is tired or when he is asked to inhale as deeply as possible. This results in suprasternal depression, and contraction of the sterno-mastoid muscles, the scalenes, as well as, sometimes, the pectoral and dorsal muscles

The most frequent form is paralysis of the diaphragm Bilateral paralysis results in the appearance of distinctive signs: simultaneous lifting of the thorax and abdomen during inspiration is replaced by a see-saw thoraco-abdominal movement, caused by inspiratory depression of the epigastrium It is more difficult to be certain concerning unilateral paralysis It will be found a good plan to compare the behaviour of the lower intercostal spaces on deep inspiration Fluoroscopic examination is particularly useful here for studying the mobility of the two halves of the diaphragm. The presence of paralysis of the muscles of the abdominal wall makes clinical interpretation difficult.

The abdominal muscles must be considered here as respiratory muscles They play a very important role in helping the diaphragm to press the abdominal mass before it; furthermore they are of great importance in forced expiration and the mechanism of coughing. Abnormal umbilical movements during the effort of coughing afford an early sign—an excellent and easily detectable one—of the involvement of these muscles.

The major bulbar form of poliomyelitis develops with a rapidity which is sometimes explosive, and it may lead to a dramatic change in a few hours The clinical picture results from the juxtaposition of nervous disturbances of a vegetative nature (major respiratory, circulatory, and vasomotor functions) mental disturbances, and paralysis of a certain number of cranial nerves

Patients with "high" poliomyelitis suffer above all from respiratory disturbances They are dyspnoeic and cyanosed, their respiration very quickly becomes difficult, and the air passages are flooded. Usually the symptoms develop so rapidly that there is some difficulty in discovering the cause of the state of asphyxia The problem is still more complex if the intercostal muscles or the diaphragm are simultaneously paralysed

When it is possible to follow the course of events, it can be seen that the difficulty in breathing is caused principally by a disturbance in respiratory command, the patient having lost the ability to modulate respiration and adapt it to his needs Respiration becomes irregular, the muscles concerned lose their synchronism, the action of the accessory respiratory muscles may be out of step (inversion of the movements of the alae nasi) Under favourable conditions it can be observed that the patient is no longer able to change the depth or rate of breathing at will This "dry" phase is short and usually followed—sometimes abruptly—by the "wet" phase The whole respiratory tract becomes gradually or suddenly obstructed Respiration is noisy The patient seems to disturb the liquids clogging the air passages with every breath Rales are heard on auscultation Sometimes the subject succeeds in discharging mucous and serous matter or a little froth These phenomena of hypersecretion almost always set in with great rapidity and in the same manner as acute oedema of the lung

Circulatory disturbances are more difficult to distinguish Tachycardia is the rule, it only becomes of significance in the absence of asphyxia, but then the progressive acceleration of the pulse is an immediate and serious sign The blood pressure is frequently unstable, and hypertensive episodes indicate a very bad prognosis Disturbances in cardiac rhythm occur at a late stage, shortly before death

Vasomotor and secretory disturbances constantly occur in this type of poliomyelitis They consist of alternate flushing and pallor of the skin, above all of the face, fits of sweating which recur several times daily, often brought on by examination of the patient Salivary secretion is exaggerated Pharyngo-tracheo-bronchial obstruction is probably aggravated by the increased secretion throughout the respiratory tract.

Disturbances of consciousness are frequent in the course of "high" poliomyelitis, they progress to coma Attacks of drowsiness often mark

Perhaps the common expression "bronchial and pulmonary weakness" may be applied to these patients better than to any others. We may speak of a "*chronic poliomyelitic lung*", *affected by disturbances of* ventilation, bronchial and pulmonary infection, and perhaps even by bronchiectasis, although the presence of the latter has not been demonstrated so far

BULBAR FORMS OF POLIOMYELITIS

During an epidemic there may appear, in addition to ordinary infantile paralysis, various morbid symptoms indicating anatomical involvement of, or functional change in, the supramedullary centres. Paralysis of the lower cranial nerves cannot be explained in any other way. Thanks to anatomical studies, such as those of Bodian [4] and Laruelle [23 21] we are aware of the *frequency and diversity of poliomyelitic lesions throughout the brain* stem and even in the highest segments of the cerebrospinal axis.

The prevalence of bulbar manifestations in poliomyelitis seems to be particularly high during certain epidemics. During the 1946 summer epidemic in Minnesota, the prevalence of bulbar symptoms (with or without spinal manifestations) was 23% among subjects under 16 years of age *and 36% above that age*

The invasion phase of this type of poliomyelitis has frequently no special feature, apart from pharyngeal phenomena and the frequency of sore throat or, more precisely, of redness and oedema of the pharynx and the tonsils The invasion phase seems shorter than in the usual form.

In 90% of cases, high localization is accompanied by spinal paralysis *—either extensive paralysis of the quadriplegic type or, more often, paralysis* predominantly or exclusively localized in the muscles of the shoulders, the upper limbs, or the respiratory muscles (diaphragm)

Exclusively bulbar forms are rare. They may sometimes be very localized an example of this is given by the isolated facial paralysis, of which there are sometimes quite extensive epidemics. Poliomyelitis may also be restricted to paralysis of the pharynx.

It must be stressed that in ordinary poliomyelitis it is not uncommon to observe some of the signs properly belonging to the "high" form of the disease. Among such signs may be cited . disturbances of consciousness including somnolence, vasomotor disturbances, disturbances of the respiratory rhythm and, fairly often, paralysis of one or more cranial nerves accompanying paralysis of the upper limbs. The prognosis is not seriously aggravated by these additional symptoms, for such slight bulbar involvement is usually regressive Nevertheless, the finding of one of these signs calls for particularly attentive surveillance.

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the onset of the disease There is a possibility of delirium (hallucinations) and, in very exceptional cases, convulsions, which occur only in the very last phase of the disease and not as an initial sign.

All the motor nuclei of the lower cranial nerves may be involved in "high" poliomyelitis

Paralysis of the trigeminal nerve is rare; in this connexion it should be noted that trismus is sometimes observed.

Ocular phenomena are represented above all by the involvement of the VIth, and, in exceptional cases, of the IIIrd nerve. Nystagmus is fairly frequent, but is transitory and without any particular prognostic value On the contrary, symptoms of ocular asynergy—each of the eyes moving independently—are a grave sign, being found in the most serious forms [42]

Unilateral or bilateral facial paralysis is not particularly serious.

Involvement of the XIIth nerve is not exceptional.

Of all forms of bulbar paralysis, by far the most frequent and most serious is that affecting the mechanism of deglutition. This form usually involves paralysis of the pharyngeal constrictors and of the soft palate, as can be detected and verified by local examination However, an accurate examination is often very difficult with such patients, and, even under the most favourable examination conditions, it may happen that paralysis cannot be definitely confirmed Nevertheless, the functional disturbances by themselves are characteristic. The first to appear is choking, fits of coughing after drinking or, more rarely, discharge of liquid through the nose Very rapidly respiratory disturbances dominate the scene. They are caused both by mechanical difficulty, due to obstruction of the glottis by pharyngeal secretions and saliva which the patient can no longer swallow, and by sudden infective accidents, progressing downwards with flooding of the tracheo-bronchial tract The patient suffocates, becomes cyanosed, and seems with every effort at breathing to disturb mucous matter in the air passages Saliva and froth, which is sometimes bloody, flows from the corners of the mouth. Clinical or radiological examination, apart from the diffuse signs of obstruction, sometimes reveals a localized area of pulmonary atelectasis Paralysis of deglutition is by itself sufficient to bring about death On the other hand, if it is recognized in time and properly treated, this form of paralysis is one of those from which recovery is most complete

Laryngeal paralysis may be frequent in poliomyelitis It may be suspected if symptoms of suffocation appear abruptly in the initial period. Later on, the symptoms become lost in the general picture of respiratory distress and it is difficult to detect them

The prognosis of the severe bulbar forms of poliomyelitis is particularly grave. However, there is still some hope of recovery in the absence of pulmonary obstruction and vasomotor disturbances causing oedema Disturbances of ocular co-ordination and a high blood pressure are especially serious Death occurs in a state of asphyxia, with cyanosis, coma, delirium, and sometimes convulsions in the final stage. The total course of the illness may last from a few hours to a few days It is exceptional but not impossible for the patient to survive more than a week, and in this event chances of recovery greatly increase When the disease takes this favourable and unexpected turn it is curious to note that all the vegetative disturbances disappear once and for all, that the sequelae are minimal or absent, and that paralysis involving the cranial nerves often clears up without leaving a trace

NON-PARALYTIC, ABORTIVE, AND INAPPARENT FORMS

Nowadays it is unanimously agreed that infantile paralysis is only one of the aspects, and certainly the least frequent one, of the infection caused in man by the poliomyelitis virus.

Classification of the particular forms of poliomyelitis which do not result in paralysis has been made difficult by the frequent confusion in the use of the terms for designating these forms This applies in particular to the terms "non-paralytic" and "abortive". The name "abortive poliomyelitis" has often been used by some authors in a broad sense to include all forms other than paralytic poliomyelitis, and by others in a restrictive sense reserved for forms of poliomyelitis with no sign of nervous-system involvement

Thus it is often difficult to interpret the results of epidemiological surveys, since the figures given refer in some cases only to non-paralytic forms (i e , those where there have been clinical signs of nervous-system involvement) and in others, to a more indefinite collection of so-called abortive forms

It can be estimated that during an epidemic lesions of the anterior horn appear in only about 10% of cases with clinically detectable signs of nervous-system involvement If the abortive cases without any nervous symptoms are added, the percentage of paralytic forms would seem hardly to exceed 1% or 2%

Recognition of the non-paralytic and the abortive forms is always difficult. In fact, on studying poliomyelitis from the viewpoint of the family of the paralysed patient several clinical aspects of the disease can be described. It is interesting to note that in these particular forms the

whole disease is reduced to one of the episodes noted sometimes during the prodromic phase and often during the invasion phase.

We suggest that the following should be distinguished: (*a*) painful forms with meningeal involvement; (*b*) pure meningeal forms; (*c*) catarrhal forms without nervous symptoms; and (*d*) inapparent forms.

(*a*) The course followed by the painful forms with meningeal involvement is sometimes diphasic. A first phase lasting a few days involves fever, headache, pharyngeal catarrh, dysphagia, redness of the throat, or coryza All the symptoms disappear for two or three days Sometimes the subject returns to his normal activities. The disease then reappears, this time with more serious signs fever, vomiting, headache, pain in the neck, *somnolence, pains, and hyperesthesia. Special importance should* be attached to pain and stiffness of the back, the most important sign in the non-paralytic forms,[1] to Lasègue's sign, to stiffness of the neck, and to Kernig's sign. All changes in the reflexes are of very great importance, but these are exceptionally so.

Recovery usually takes place within three or four days Febrile forms lasting up to 14 days have been reported, and very slight paralysis may possibly be found The latter would represent the extreme limit of the paralytic form (embryonic type of Muller poliomyelitis)

Examination of the spinal fluid is invaluable in diagnosing these forms As early as 1912, Peabody [34] reported that there was a lymphocytic reaction in the abortive form Since then systematic studies, such as those of Nissen,[32] have shown the very great frequency of changes in the spinal fluid in the non-paralytic forms In the absence of sufficiently systematic studies, it cannot be affirmed that they exist in every case It may be estimated that they will be found in between 50% and 80% of cases and perhaps more, if care is taken to repeat the lumbar punctures when necessary. The cellular reaction is of the lymphocytic or mixed lympho-polynuclear type It may be delayed with respect to the clinical onset, and, if the temperature curve is diphasic, it appears only with the second rise in temperature As in infantile paralysis, late albumino-cytological dissociation can sometimes be detected.[41]

(*b*) The pure meningeal form is one of the most interesting aspects of non-paralytic poliomyelitis [31]

Of all the non-paralytic forms of poliomyelitis, meningitis is the most difficult to diagnose on merely clinical data A certain number of arguments seem of value. Apart from the epidemiological conditions, the circumstances in which the disease appears and negative findings from investigations of other possible causes of lymphocytic meningitis, the following indications are of value a diphasic temperature curve; intensity of the pains: pain in the back, Lasègue's sign; mild but distinct paresis; and

the disappearance of a reflex The spinal fluid shows moderate pleocytosis (about 150).

An initial polynuclear reaction may be found, but it cannot be considered as pathognomonic in the present state of knowledge Stress has been laid on the abnormally long persistence of hyperalbuminosis in the spinal fluid after three, four, five, and even seven weeks, and even on the secondary increase in the protein content [41]

(c) Catarrhal forms without nervous symptoms constitute a group of abortive forms which seems to be very frequent There is no doubt that this is the most common way in which infection by the virus of Heine-Medin's disease shows itself When a careful enquiry is made in connexion with a subject suffering from infantile paralysis, it is not uncommon to find that children or adults in close contact with the patient have suffered from some mild illness, very often so slight that they have continued with their normal activities—e g , a slight fever, vague pains, slight indisposition, headache, or coryza The throat may be reddened, or it may be that digestive upsets with diarrhoea have broken out in the neighbourhood, sometimes even taking epidemic form

Subjects who have shown such symptoms are usually considered to have had an attack of influenza, seasonal diarrhoea, or simple sore-throat —all the more so since clinical examination, even when the contact is known, is unable to reveal the slightest neurological abnormality In a few days there is a complete reversion to normal, and the incident is forgotten It is known, however, that systematic search for the virus in such subjects is very often successful and that in some fortunate instances such a search has coincided with the appearance of the virus in the patient's stool.

If, furthermore, the spinal fluid is systematically studied during the course of these benign affections, then, in addition to those cases where the results are negative (just as in the comparable episodes which occasionally occur in the prodromic phase of common infantile paralysis), there are cases where distinct changes can be found (lymphocytosis)

(*d*) The inapparent forms, i e , those which do not reveal their presence by any detectable morbid symptoms, are probably the most frequent. Clearly, exceptional circumstances and well-directed, systematic research are necessary if the actual existence of the inapparent forms is to be demonstrated

CONCLUSION

The symptoms and signs of paralytic poliomyelitis are very distinct and diagnosis of this form of poliomyelitis may be made with certainty. Diagnostic confusion with diseases resembling poliomyelitis should be

rare, if the patient's history is carefully analysed and the clinical signs and changes in the spinal fluid (cells, protein) compared with those present in other diseases

On the other hand, the clinical diagnosis of the non-paralytic forms is still usually a presumptive diagnosis which, although highly probable, is not certain In this field, clinicians are impatiently awaiting a simple, early, and practical diagnostic test.

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THE MANAGEMENT OF ACUTE POLIOMYELITIS

W. RITCHIE RUSSELL, M D., F R C P

Consultant Neurologist to the United Oxford Hospitals, Oxford, England

The management of acute poliomyelitis may sometimes require no more attention or care than is needed for a patient with a feverish cold, but on other occasions the services of several specialists and nurses may be needed to save the life of a single patient

Pre-Hospital Care

Diagnosis

The diagnosis of poliomyelitis can rarely be made with certainty until or unless paralysis develops This occurs during the meningitic stage of the disease which has been called by Horstmann [6] the *major illness* Four or five days before the major illness begins there is, in about half the cases (Russell [14]), a *minor illness* which consists usually of non-specific catarrhal symptoms which will attract little attention except during local outbreaks of the disease.

These non-specific minor illnesses are important from the point of view of epidemiology, but often it is only when they are followed by a meningitic stage that the probable nature of infection can be recognized Recent research by Melnick & Ledinko [11] confirms that for every known case of poliomyelitis there are over 100 unnoticed infections with poliomyelitis viruses which, though subclinical, nevertheless stimulate the development of natural immunity to the viruses concerned These minor illnesses are therefore beneficial to the individual if they provoke the development of immunity and do not lead to the major illness and paralysis

Horstmann & McCollum [7] have shown that the virus may be found in the blood of contacts who have a minor illness, or even sometimes when there are no symptoms at all It is thus evident that minor catarrhal symptoms during an outbreak of poliomyelitis must often be associated with poliomyelitis virus infection of the blood-stream

The minor illness

Since the diagnosis of the minor illness can rarely be made with any confidence except in retrospect, the treatment is far from satisfactory. One can only advise that catarrhal illnesses be treated cautiously during an outbreak of poliomyelitis, and that this attitude of caution be prolonged for a period of a week after the illness—for it is known that when a major illness follows it generally does so at an interval of about four days after the minor illness.

As no antibiotic is yet known to be effective against the poliomyelitis virus, treatment can only be directed towards avoiding anything which reduces the natural resistance of the nervous system.

Here we lack precise knowledge, but there is clear evidence that various forms of peripheral trauma interfere with the resistance of the central nervous system (CNS), especially of that part of it in closest connexion with the site of injury. Thus, tonsillectomy at this stage may be followed by bulbar poliomyelitis, inoculations may be followed by paralytic poliomyelitis affecting especially the limb used for the injection, and operations on limbs may have the same effect.

The dangers of physical activity during the major illness are clearly established, as will be mentioned later, but the effect of fatiguing exercise during the minor illness is not so certain. However, there are so many instances of the major illness following immediately on excessive physical activity (Russell [14]) that the avoidance of severe exercise for a few days after the minor illness probably increases the likelihood of the infection's remaining abortive without CNS involvement.

If there is evidence, therefore, to suggest the occurrence of the minor illness, then surgical operations and parenteral injections of all kinds should, if possible, be postponed Further, it is desirable that physical activity should be minimal for at least a week after the symptoms of the suspected minor illness have subsided.

The major illness

The major illness is the critical stage of the disease, and careful supervision of the patient is vitally important, for emergencies may develop with little warning, although of course many patients are never seriously ill and require no specially skilled treatment.

One of the chief difficulties in treating the onset of the major illness depends on the common failure to diagnose the condition correctly. Here the great variability of the clinical picture causes many difficulties. The chief pre-paralytic symptoms may be referred to as spinal, and consist of various pains and paraesthesias referred to the spine, trunk, head, or limbs

(Russell[14]). Many of the patients, however, do not feel ill when the spinal pains develop, and it often does not occur either to them or to their doctors that these may be the early symptoms of a serious illness.

This is a most dangerous situation, for there is clear evidence adduced by Russell[12, 13] and Horstmann[8] that the continuance of even limited physical activity is harmful at this phase of the disease and increases the severity of the paralysis which develops.

Immediate bed-rest after the onset of the major illness is therefore vital and seems to be the most powerful therapeutic measure at the clinician's disposal. Unfortunately the patient often consults his doctor too late, having remained active after the onset of symptoms Such a patient when first seen may not yet have developed any paresis, and yet the fate of the spinal-cord cells may already be decided. The patient may not appear particularly ill and the physician in such circumstances is liable to consider that the developing paresis will not be severe It must be emphasised, however, that it is not possible to assess from the pre-paralytic clinical picture the extent to which paralysis will advance, so that all paralytic cases must be watched carefully, since any one of them may develop critical complications The history as regards the continuation of physical activity after the onset of the major illness is, indeed, the only clinical point of prognostic value, and this is not always a reliable guide

Treatment of the pre-paralytic stage of the major illness consists, therefore, of absolute rest in bed Known antibiotics are ineffective and gamma globulin is also ineffective at this stage, as the virus is already in the nervous system It is conceivable that future research may discover some substance which interferes with nerve-cell metabolism in such a way that it is rendered unsuitable for virus multiplication and can thus be saved from destruction even at this late phase of the disease. Under present conditions and existing knowledge, however, the fate of the nerve cells is probably often decided before the nature of the illness is recognized.

Transfer to hospital

During outbreaks of poliomyelitis many cases are admitted to infectious disease (ID) hospitals before any paralysis appears and may then develop paralysis after admission to hospital. This admission of the pre-paralytic case is often advocated for reasons of isolation, but for the patient it may have grave objections In the first place, transfer to hospital involves a journey which may be both physically exhausting and psychologically terrifying, at a stage when absolute physical rest and mental relaxation may together prevent paralysis from developing. On the other hand, the development of bulbar or respiratory paralysis at home may prove to be

quickly disastrous, and in addition it is extremely important to diagnose without delay cases of, say, meningitis, or other types of acute neurological disease.

If the diagnosis of poliomyelitis is reasonably certain before any paralysis appears, then there is much to be said for keeping the patient quietly at rest at home, provided home conditions are good (Stimpson[14]). This is an anxious matter, and the doctor is well advised to share the responsibility for such important decisions with a colleague. In this connexion there is a special need for mobile teams of doctors to help with these decisions, to carry out special tests such as lumbar puncture, and to maintain artificial respiration when necessary during transfer to hospital.

Isolation precautions are desirable, though their effectiveness in this disease has never been fully established The typhoid type of precautions are appropriate, and some authorities advise isolation of contacts for a period of from two to three weeks, especially in the early cases of an outbreak when there is sometimes evidence of a narrow stream of infection (Francis,[4] Bradley[1]) which should be to some extent controllable by public-health measures However, in other outbreaks the virus seems to be very widespread and only becomes apparent by affecting scattered individuals who presumably have less immunity or are exposed to an excessive quantity of virus

Organization of Hospital Treatment

It is obvious that the great majority of cases of suspected paralytic poliomyelitis should be treated in hospital, but it is difficult to provide adequate hospital facilities, especially where there is insistence on the transfer of all cases to ID hospitals which are often inadequately staffed [illegible] lical wards allotted [illegible] has for long been [illegible] s to an increased risk of cross-infection.

During an epidemic of poliomyelitis a considerable proportion of cases sent to the receiving hospital will have been wrongly diagnosed. Not only are conditions such as subarachnoid haemorrhage, cerebral thrombosis, acute infective polyneuritis, and hysteria or pressure palsy sent for admission, but also the dangerous varieties of meningitis, which require very urgent specific treatment.

[illegible]

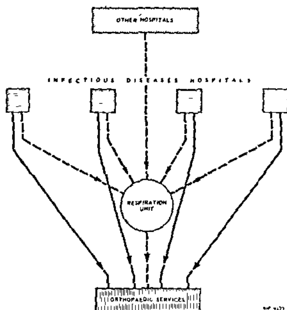
in good condition may quickly develop these critical complications The only safe way to deal efficiently with all these disturbing possibilities is for an experienced physician to see the case "on the door-step" of the hospital, or to visit the patient in his home first.

Adequate hospital care for acute poliomyelitis therefore requires careful planning and provision for a variety of emergencies.

Special respiration unit

In addition to these general arrangements for hospital treatment, it is now considered necessary to develop a few highly trained units which can take charged of the specially difficult cases of respiratory insufficiency (see fig. 1). Anaesthetists play a big role in such a unit, and one unit can normally serve several hospitals admitting poliomyelitis provided the unit can form a mobile team whose members can transport difficult cases to

FIG 1. SUGGESTED PATTERN OF HOSPITAL CARE FOR POLIOMYELITIS IN A COMMUNITY OF ONE MILLION PEOPLE



Four hospitals are chosen to admit acute cases A small respiration unit of, say, six beds is established in relation to the largest hospital in the region, and receives specially difficult cases from all hospitals All hospitals transfer cases requiring prolonged treatment to orthopaedic hospitals

the hospital chosen as the headquarters of the respiration unit. Such a unit can deal effectively with sporadic demands, and though it may be overwhelmed in a serious outbreak its highly trained personnel form a nucleus of experience and knowledge which will be invaluable in dealing with the unexpected local outbreaks which may cause so much difficulty.

Supervision of the spread of paralysis

There is no known means of determining the patient's prospects during the pre-paralytic phase, so that it is necessary to watch all cases carefully until the spread of paralysis ceases. Only by so doing can the development of dangerous complications be recognized in time to prevent the occurrence of disasters such as the inhalation of vomit, or massive lung collapse.

The prompt recognition and treatment of dangerous complications should be the first aim of every unit admitting acute cases Other aspects of treatment, such as care of the limb muscles in the acute stage, are of subsidiary importance This view requires emphasis, for some small hospitals still consider that their chief function is to isolate patients and " to hope for the best ", without making any serious attempt to provide for dangerous complications.

One of the greatest problems is to ensure that cases of spreading paralysis are watched by doctors and nurses who are already well versed in the problems which may arise Such close personal supervision is required throughout the 24 hours that it is often desirable that an experienced doctor should be within two minutes' call both day and night Sharp outbreaks of poliomyelitis often appear in areas which have had little experience of the disease for many years, while a local outbreak is often followed for several years by a low incidence in that area Hence those who have acquired good experience of the disease are often not in the right place to be able to help with the next outbreaks The difficulties, therefore, are formidable, but clear recognition of the problems should facilitate the discovery of a solution appropriate to varying local conditions

Principles of Nursing Care

There are very few diseases in which the nurse plays a more important and more responsible part in treatment than acute poliomyelitis.

In the first place, many of the patients arrive fully conscious and very frightened. The nurse should therefore show that confidence and efficiency which allay fear and allow the patient to relax, both physically and mentally Both physical and mental rest are extremely important in the pre-paralytic phase (Russell[14]) and heavy sedation with barbiturates is

often advised, provided that bulbar symptoms are not prominent (Brehme & Leuterer[2])

The nurse should observe, record, and report the following points

(1) temperature

(2) pulse, including rate, rhythm, and volume

(3) rate, depth, and character of respiration; waking and sleeping chart at least four-hourly; any use of accessory muscles of respiration (alae nasi, sterno-mastoids)

(4) difference between waking and sleeping respiration

(5) colour

(6) mental alertness and responsiveness

(7) refusal of food, dysphagia, nasal regurgitation, vomiting

(8) speech disturbances, in particular nasal voice and loss of voice power

(9) bladder and bowel function, with intake and output chart as required

(10) weakness or paralysis of any part

(11) positions spontaneously adopted by the patient, and sites of pain, spasm, and tenderness

Poliomyelitis bed

The patient's bed should be specially planned A fracture bed-board is required to keep the mattress quite fast The mattress should be 4-6 inches (approximately 10-15 cm) shorter than the bed A foot-board should be held beyond the mattress by two 4-inch (10-cm) wooden blocks Pillows are better avoided entirely Blankets should be few and light to avoid all sense of constriction on the body or limbs The ward should be kept at a temperature of not less than 65°F (18 3°C)

A good supply of small pillows and pads should, however, be available to provide local support to joints which are uncomfortable For example a soft pad under the neck, under the small of the back, or under the knees allows the patient to relax in greater comfort

Posture and passive movements

A large part of the nurse's effort is at first directed towards making the patient as comfortable as possible and she should never tire of making small changes in position which will often give temporary relief

A complete change of posture is desirable every two to four hours, especially when there is any weakness of the muscles of respiration The

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to instructions such as:

"Press your elbows down to your sides and hold them there" (shoulder-fixing muscles);

"Pull your hands up to your face" (biceps);

"Push my hands away" (triceps),

"Squeeze my fingers hard" (forearm muscles);

"Spread out all your fingers and don't let me press them in" (small muscles of hands)

Each movement is resisted by the examiner in order to estimate the degree of weakness

Lower limbs: The lower limbs have to be examined one at a time, and it should be remembered that the weight of the limb interferes with muscle-group testing much more in the lower limb than in the upper. During testing, therefore, the examiner will, in cases with weakness, find it necessary to support the weight of the limb with one hand under the knee and one at the ankle, while he asks the patient to try as follows:

"Pull up your knee as much as possible" (thigh and knee flexors);

"Push your leg out straight" (thigh and knee extensors),

"Press your leg down towards the bed" (thigh extensors),

"Pull your toes towards you" (dorsiflexors),

"Push down" (plantar flexors)

In this way the main muscle groups can be tested in a few minutes, and examination can often be adequately carried out even with the patient lying on his side Examination may be greatly hindered by muscle tenderness, and may then have to be modified considerably.

Paralysis of pharynx and larynx

The muscles of the pharynx and larynx, even in health, maintain a precarious separation between what is intended for the oesophagus and the free passage of air to lungs The slightest paresis or dysfunction of this mechanism leads to a highly dangerous state of affairs, hence, there is an imperative need for all those concerned with poliomyelitis to understand how these disorders may be recognized and how they should be treated A conscious adult will, of course, report difficulty in swallowing or speaking, but "bulbar" cases are often unconscious, and under these circumstances pharyngeal paralysis is quickly fatal if not recognized. Fortunately, recognition is usually easy as the patient's every breath is heard to bubble or rattle through a pool of mucus if the patient is lying

lateral and semi-prone postures are specially suitable. Lying on the back (supine) should seldom be allowed if there is weakness of the muscles of swallowing or of respiration, owing to the danger of inhaling secretions or vomit in this position.

Most patients are very sensitive to movement of any kind, but if they are left for long in one position this hyperaesthesia is likely to become worse Hence the nurse should take every opportunity to move the patient's limbs, short of causing much pain—indeed, she should be carefully instructed in passive movements to all the main joints and muscle groups so that these movements can be repeated both day and night when the physiotherapists are rarely available Frequent passive movements and changes of posture ultimately increase the patient's comfort, and prevent the development of tight muscles ("muscle spasm") Changes of posture from one side to the other are specially important in cases of respiratory weakness, as they reduce the danger of pulmonary complications. Rigid splinting should be avoided as prolonged immobility of a paralysed muscle is always harmful

Physical examination

The methods of examination required for the diagnosis of paralytic poliomyelitis are not considered here, but it is necessary, as part of the management of the acute disease, to examine the appropriate strength of the chief muscle groups, especially during the early days of the disease This examination in the acute stage should on no account be fatiguing, so that it must be neither detailed nor too lengthy The chief muscle groups of the body can all be tested roughly (see below) within a period of about two minutes, and this should only be done two or three times daily

It is essential, also, that a close watch be kept on the state of the respiratory muscles

Examination of upper and lower limbs

During the acute stage the strength of the extremities is examined for two chief reasons, first, to recognize gross paralysis, and second, to follow the course of the paralytic process to the point where it stops spreading The muscles are examined during the major illness as little as possible, but a few tests should be carried out once or twice daily to ascertain the general distribution and severity of paralysis. In the infant, the mere act of lifting up a limb will stimulate various muscles to contract, and muscle groups which fail to contract are generally easily identified through watching and gently resisting the spontaneous movements of the limbs.

A skilled team of nurses can put a patient in a modern tank respirator without either physical or psychological trauma. Many patients are frightened by the appearance of the machine, but in fact there is no need for this, as the patient can be lifted on to the respirator stretcher without being given a chance to see the machine as a whole. The practice use of the respirator allows plenty of time to get the collar and other adjustments comfortable and the patient can lie on the respirator stretcher whether the machine is being operated or not Should artificial respiration prove to be essential, the value of this preliminary practice will be very obvious.

Hot packs

Disciples of Sister Kenny maintain that hot packs to the chest improve breathing in some cases. The effect on the vital capacity of this procedure has not been measured and obviously it can make little contribution to the severe forms of paralysis; in any case, the weakened muscles can be rested only by mechanical means In the writer's view the use of hot packs at this spreading stage of the disease is likely to distract a busy nurse's attention from more urgent and vital matters For this reason hot packs should be avoided while the patient's life is in danger.

It is, of course, obvious that the true state of the respiratory muscles can be assessed only when the airways are clear and the lungs healthy. Some patients with intercostal paralysis also have atelectasis. In dealing with this grave state of affairs there must be no hesitation in using the tank respirator or positive-pressure intratracheal breathing, even if preliminary bronchoscopy is not possible high respiratory rates and pressures are often necessary in these cases, and, fortunately, areas of collapsed lung which occur commonly in respirator cases usually resolve successfully in a period of three or four days.

Reflexes and sensation

A very cursory examination of sensation will suffice unless, of course, there is any possibility that some other form of acute spinal disease is causing the paralysis The tendon reflexes disappear as paralysis develops, and this provides a valuable confirmation of genuine acute lower motor neurone paralysis The plantar response is either absent or flexor. The abdominal reflexes are absent if the abdominal muscles are weak.

Sphincter control

Retention of urine is an important early symptom in some cases, so that bladder distension must not pass unobserved.

on his back (supine), and his condition quickly improves with adequate postural drainage in the semi-prone position; indeed, when this posturing has cleared the upper airways of the obstructing secretions, the true state of respiration may be judged.

Another symptom of pharyngeal paralysis is simply that a child may refuse to eat or drink. This refusal may be misinterpreted by the parents, with disastrous consequences

In these bulbar cases the muscles of the face, jaw, and eyes may also be affected, but these are relatively unimportant. Coma is also frequent, but though this is alarming, cases of this kind often make a complete recovery without any permanent paralysis. Hence the patient (often a child) *who is deeply unconscious with poliomyelitis is often the most* rewarding case to keep alive.

Respiration

Progressive weakness of the muscles of respiration is a most alarming experience for the patient and may lead to a panic reaction which may be tragically and cruelly misjudged The voice becomes feeble and the cough ineffective The respirations become shallow and rapid, and the patient can speak fewer and fewer words between breaths Mere inspection of the chest and abdomen indicates to the experienced physician whether the intercostals and diaphragm are providing adequate inspiratory power Feebleness of coughing denotes paralysis of the abdominal muscles which are the main muscles for coughing Such abdominal paresis is usually associated with trunk weakness which makes it impossible to move about in bed, and may be tested by palpating the abdominal muscles during coughing or while the patient attempts to raise the head off the bed.

During the phase of spreading paralysis some measurement of vital capacity is essential if an approaching need for artificial respiration is to be recognized in good time A spirometer is the best measure for this, but the patient's maximum count in one breath also provides a very useful measure of vital capacity, and enables any change to be quickly appreciated. The healthy person can easily count to over 40 with one breath, and therefore when the total which can be counted drops below 10, or the vital capacity drops below 1,000 cm^3, preparations should be made for providing some form of assisted respiration

When there is no pharyngeal weakness, a tank-type respirator should be used and the patient should be put in the machine for practice purposes —this rests the muscles of respiration at a critical stage of the disease, and, if well managed, gives the patient both physical and psychological relief

FIG. 2. SEMI-PRONE POSITION, WITH BED TILTED FOR DRAINAGE

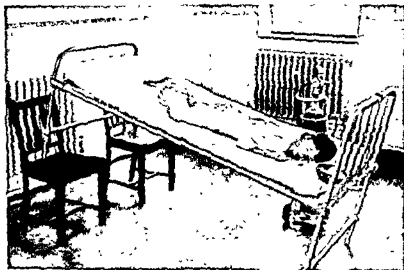
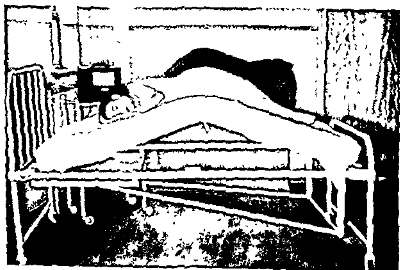


FIG 3. INVERTED-V BED ADJUSTABLE FOR POSTURAL DRAINAGE; A THROAT MICROPHONE AND LOUD-SPEAKER ARE IN USE[15]



Special Problems

Bulbar poliomyelitis

The vital importance of recognizing pharyngeal paralysis has already been stressed, and the nurse should learn how to differentiate between the shallow and guarded respiration associated with mechanical blockage of the airways, and that due purely to paralysis of the muscles of respiration or involvement of the respiratory centre.

In all forms of respiratory embarrassment, however, the airways must be kept clear, from the practical point of view, the nurse must always do everything in her power to ensure that there is no obstruction to respiration, and, this done, the state of the patient will indicate whether the strength of respiration is adequate for the patient's needs.

A large proportion of bulbar cases can be nursed successfully and safely without requiring either artificial respiration or tracheotomy, but provision must always be at hand for carrying out these further procedures at short notice

Careful posturing is life-saving when there is paralysis of the pharynx, *and should be instituted in the home or ambulance as soon as the dangers* of inhalation are recognized (see fig. 2). These cases are often children, who, if left unattended, will frequently sit up and inhale vomit: this often leads to fatal pulmonary collapse

Nursing on the back (supine) is always dangerous in bulbar cases unless the bed is tipped very steeply The patient should have a firm mattress with no pillow and should be turned on his face or lie semi-prone. Raising the foot of the bed 18 inches (about 45 cm) is a most valuable addition from time to time to facilitate drainage Inverted-V bronchiectasis beds are specially useful (see fig 3) The lateral posture may also be used, and the tilted posture may at times be relaxed for nursing or other reasons, provided it can be re-established within a second or two should the child, for example, vomit unexpectedly or choke while attempting to swallow. A simple harness around the child's shoulders and secured to the foot of the bed prevents him from sliding out of position when the bed is steeply tilted.

During the period of pharyngeal paralysis the patient's every breath should be listened to, preferably with the assistance of a throat microphone (see fig. 3) so that any accumulation of secretions in the upper air passages may be promptly recognized, and irregularity or failure of respiration, or retching, quickly observed. The nurse herself can deal with minor accu-

It may be helpful to read the blood pressure every 15 or 30 minutes for a rise is often an early sign of carbon dioxide retention

The regular use of an oximeter may be useful in this type of case, as it will demonstrate moderate degrees of hypoxia for which mere inspection of the patient's colour is an unreliable indicator.

"Combined" cases

The combination of bulbar paralysis with spinal paralysis of respiration requires highly specialized care in a respiration unit, and in the writer's experience Professor Lassen's method[9] is the treatment of choice for this most difficult group of cases (see also page 157).

Respiratory paralysis without bulbar involvement

Fortunately, the majority of cases of spinal respiratory paralysis have no paralysis of swallowing, and for such patients the tank respirator usually provides the best method of supplying artificial respiration.

Not long ago the usual practice as regards respiratory failure was to wait until the patient was severely anoxic before using a respirator. This, however, increases the danger of atelectasis and is inconsistent with the general attempt to rest muscles during the acute stage of the disease. As has already been stressed, there is therefore much to be said for early respirator treatment before the patient becomes seriously embarrassed, but this should be done by nurses trained to transfer a patient into a respirator without inflicting either physical or psychological trauma It has been mentioned that two special nurses may be required for one patient, but three or four additional people may be required to put a patient in a respirator or to change his position. The new Siebe-Gorman respirator (see fig 5) with split front considerably simplifies nursing problems.

The detailed care of respirator cases from the nursing point of view has been described in publications of the National Foundation for Infantile Paralysis, Inc, New York, N.Y., USA[8]

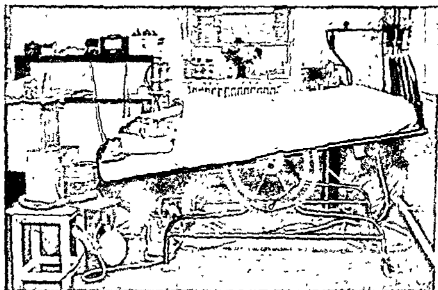
The following points require special attention:

(1) Correct adjustment of operating pressures While the lungs are healthy, hyperventilation may easily be produced Pressure of about —16 cm, and +5 cm of water at a rate of 16 cycles per minute, are often suitable for older children and adults provided the lungs are reasonably healthy When one lung is collapsed a much higher rate may be required —up to 35 cycles per minute, and even higher in infants.

(2) The airways must be kept clear by suction and posturing. Frequent changes of position, including the semi-prone posture, can be obtained

mulations of secretions by increasing the tilt of postural drainage (see fig 4) and using the sucker. However, there should also be immediately available a doctor versed in the methods of aspirating the trachea, and one who can perform the operations of bronchoscopy, laryngeal intubation, or tracheotomy.

FIG. 4. QUICK-TILTING BED IN USE FOR A CASE OF SPINAL AND BULBAR POLIOMYELITIS SUCCESSFULLY TREATED BY A RESPIRATION PUMP THROUGH AN INTRATRACHEAL TUBE



As has already been mentioned, many bulbar cases retain adequate strength in the respiratory muscles, but careful watch must be kept not only for weakening of the respiratory muscles, but also for failure of the respiratory centre. In cases with respiratory muscle weakness the development of atelectasis may immediately precipitate a crisis, as the muscles may at once *become inadequate for the reduced available lung tissue*. Any of these developments may require the use of artificial respiration, but the point at which this becomes necessary is difficult to recognize. The difficulty is greatest when the patient's consciousness is clouded, as it is then uncertain whether the mental dulling is due to cerebral hypoxia or to the focal effect of the virus on brain-stem centres. Anxiety in these cases is increased by the knowledge that the use of a respirator in the presence of pharyngeal paralysis is most dangerous owing to the machine's sucking secretions into the lungs.

It may be helpful to read the blood pressure every 15 or 30 minutes for a rise is often an early sign of carbon dioxide retention.

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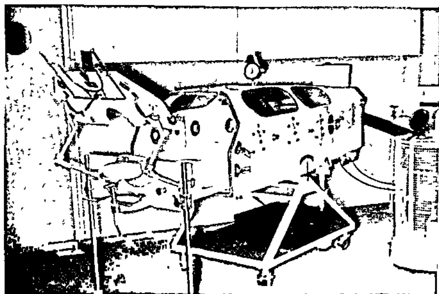
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FIG. 5. SIEBE-GORMAN RESPIRATOR PARTLY OPENED TO ILLUSTRATE THE "SPLIT FRONT" WHICH GREATLY FACILITATES NURSING CARE



in the newer respirators and are highly advantageous *The breath-sounds* at the larynx should be frequently listened to in order that pooling of secretions may be recognized in time The nurse may use a stethoscope for this, but a throat microphone [a] amplified by a loud-speaker is greatly preferable (Stott [17])

(3) The adequacy of oxygenation may be checked by an oximeter,[b] but frequent blood-pressure readings should also be taken, as a rise of blood pressure is an early sign of carbon-dioxide retention.

(4) Every precaution should always be taken to avoid atelectasis, and daily lung x-rays may be desirable Bronchoscopy may be required, while any loss of functioning lung-tissue may necessitate increasing the pressures and rate at which the respirator is working.

comfortable when the respirator is opened. The Oxford Inflator (Macintosh & Pratt [10]) is convenient for this purpose and, being operated by

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[a] Obtainable from Isis Equipments, Broad St , Oxford, England

[b] Manufactured by Stanley Cox Ltd, 11 Gerrard St , London W 1 , England

hand, can be made to synchronize with the rhythm of the respirator before the machine is opened. Mechanically operated respiration pumps may be very useful for this purpose (Russell & Schuster[15]).

Complications

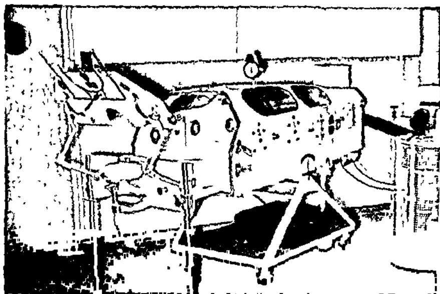
Atelectasis

The development of pulmonary atelectasis is feared in all cases requiring treatment for any form of respiratory insufficiency, and measures required to minimise this serious danger are of the first importance. If frequent turns from side to side, and the maintenance of a clear airway, are insufficient, percussion and vibration to the chest by the physiotherapist can be of great value in clearing a collapsed lobe (fig 6) Bronchoscopy must

FIG. 6 PHYSIOTHERAPY TO A PATIENT RECOVERING FROM RESPIRATORY PARALYSIS WHO HAD BEEN SUCCESSFULLY TREATED BY POSITIVE-PRESSURE BREATHING THROUGH A CUFFED TRACHEOTOMY TUBE



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(5) A good respirator is so constructed that most nursing can be carried on without opening the respirator, but in addition it is essential that an efficient form of positive-pressure breathing be available to keep the patient comfortable when the respirator is opened. The Oxford Inflator (Macintosh & Pratt [10]) is convenient for this purpose and, being operated by

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THE MANAGEMENT OF RESPIRATORY AND BULBAR PARALYSIS IN POLIOMYELITIS

H C A LASSEN, M D.

Professor of Epidemiology, University of Copenhagen
Chief Physician, Department of Communicable Diseases, Blegdam Hospital, Copenhagen

It is quite striking, considering the enormous literature on poliomyelitis, that so comparatively little has been written about the life-threatening forms of the disease, their prevention, and their treatment This probably has to do with the fact that optimal treatment of bulbar poliomyelitis with or without respiratory failure is one of the most complex therapeutic problems in the whole field of medicine Until recently, mortality was discouragingly high everywhere. Time is short in bulbar and respiratory poliomyelitis Formerly, this was only poorly understood, but thanks to the work done especially in the USA [24, 25, 39, 67] it is now universally accepted that the all-important problem in life-threatening poliomyelitis is respiratory—a problem of keeping up adequate oxygenation and securing proper elimination of carbon dioxide.[23, 24, 25] If ventilation is failing, this may be due to weakening of the respiratory muscles or involvement of the autonomic medullary centres, but very often blocking of the airway with plugging of bronchi, atelectasis, pneumonitis, and pulmonary oedema will be the most important underlying factors when the syndrome of inadequate ventilation develops.[61] It was formerly thought that patients with bulbar and respiratory poliomyelitis died because of overwhelming, intractable "bulbar" virus infection, i e, infection of the medulla oblongata, pons, and midbrain This caused an understandable therapeutic defeatism

There is, in fact, no doubt that many of these patients do have widespread lesions in these parts of the central nervous system (CNS), but the newer concept of bulbar and respiratory poliomyelitis as chiefly a problem of maintaining an unobstructed airway has proved therapeutically very successful.[24]

Bulbar poliomyelitis with respiratory failure is still a very grave disease, yet mortality-rates have been reduced considerably since the introduction

Manual ventilation was administered with the aid of medical students working in relays For many weeks we had 250 students coming in daily, 600 trained nurses, and hundreds of auxiliary personnel

Naturally this method is neither new nor ideal, but in the circumstances it proved of great value, and for transportation of patients to a treatment centre it certainly has its good points

BIOCHEMICAL ASPECTS OF BULBAR AND RESPIRATORY POLIOMYELITIS

Involvement of the autonomic respiratory centres, weakness of respiratory muscles, obstruction of the airway, and secondary bacterial infection—or a combination of these—all tend towards reducing ventilation with ensuing decrease of oxygen saturation and reduced elimination of carbon dioxide Anoxia and hypercapnia do not always run parallel, however: they should be discovered and counteracted before too much damage has been done [illegible]
of decreased oxygen satu [illegible]
saturation has come dow [illegible]
been done to the motor cells of the central nervous system, especially when they are the site of virus infection [58] Direct measurements are naturally the best means of evaluating arterial oxygen saturation if hypoxia is suspected, but as repeated arterial punctures are not practicable it may often be of considerable value to use the Millikan oximeter, although this, of course, gives only the relative values and cannot be used continuously for prolonged periods of time Even if the importance of oxygen lack in bulbar and respiratory poliomyelitis has been generally appreciated these past ten years, the deleterious effect of carbon dioxide retention and respiratory acidosis has been less well understood As will be described later, this condition, too, is difficult to single out in the maze of symptoms seen in patients with life-threatening poliomyelitis. For these and other reasons, the aid of a well-equipped laboratory is of inestimable value for the optimal management of bulbar and respiratory poliomyelitis [14]—especially if clinical experience is not great After familiarity with the different clinical syndromes appertaining to incipient anoxia, hypercapnia, vasomotor shock, and the virus infection itself, has been achieved, and they have been correlated with laboratory findings, the use of laboratory tests may eventually be somewhat reduced, but it takes some time, and clinical judgment is certainly not infallible.

By definition, clinical acidosis and alkalosis are exclusively related to variations in the pH of the blood exceeding the normal range, which for

of prompt and vigorous therapy directly aiming at maintaining an unobstructed airway

In the Blegdam Hospital we had, up to 1952, treated about a hundred cases of poliomyelitis with bulbar and respiratory involvement, mostly in cuirass respirators and invariably with very poor results, the lethality never being under 80%[46] In 1948 early tracheotomy was introduced in cases with *pooling of secretions in the hypopharynx and upper airway. This did* not improve our results.

In 1952 the catastrophe came.[33, 34, 35, 36] The metropolitan area of Copenhagen, with a population of 1 2 million people, was struck by an epidemic of poliomyelitis unprecedented in the history of Denmark, in size as well as in severity.[28] This area is served by a single hospital for communicable diseases, the Blegdam Hospital, with about 500 beds, and from the beginning of August 1952 till the end of the year we received about 3,000 patients with a diagnosis of polio, in 2,300 of whom poliomyelitis could be verified More than 1,000 had paralysis, and no less than 349 of these had pooling of secretions in the upper airway, or respiratory insufficiency, or both, requiring special therapeutic measures

It was thus a terrific fulminant epidemic, even worse than the 1946 epidemic in Minnesota and by far the worst ever recorded in Europe

At the outset we had only one tank respirator and six cuirass respirators, and naturally this meagre supply of mechanical respirators was exhausted before long Very soon our position became so desperate that the intolerable situation arose where we had to choose which patient to treat and which not to treat Patients kept pouring in week after week in great numbers—30-50 daily, of whom from six to twelve were drowning in their own secretions

The situation certainly called for improvisations, and as it was felt that application of modern anaesthesiologic principles to the problem of airway obstruction and muscular respiratory insufficiency in our desperately ill patients might be of value, anaesthesists were invited to join our staff, and from 27 August an emergency method was introduced

The emergency method consisted in high tracheotomy with introduction of an inflatable rubber cuff-tube in order to seal off the air-passage from the hypopharynx, postural drainage with frequent aspiration of the airway, and manual ventilation with a mixture of about 50% oxygen from a rubber bag Pure oxygen was used only when gross cyanosis was present, and only for limited periods of time, in order to prevent oxygen poisoning.[1, 48]

purposes, increased pCO_2 may be taken as an expression of respiratory acidosis, or hypoventilation, whereas lowered pCO_2 may be said to express respiratory alkalosis or hyperventilation. On the other hand, deviations of more than $\pm$ 2 5 millimol from a normal alkali reserve may be taken to signify metabolic alkalosis (+) or acidosis (−) If in such cases the pH is within normal range, the situation may be said to be compensated, which is quite often the case, yet, as stated above, hypoventilation or hyperventilation in terms of CO_2 may be present, indicating therapeutic measures. As we have so far no dependable devices for instantaneous determination of alveolar CO_2 levels, we still have to take CO_2 measurements of the arterial blood, which is troublesome

Apart from lowered oxygen saturation and abnormal carbon dioxide tension, certain biochemical changes may occur in bulbar and respiratory poliomyelitis Thus, a decreasing total protein content of the plasma,[8] with inverse albumin-globulin ratio, is very common, as are biochemical changes due to renal insufficiency, but since these are of only secondary therapeutic importance in the management of bulbar and respiratory poliomyelitis they will not be discussed here in detail

CLASSIFICATION OF LIFE-THREATENING POLIOMYELITIS

Unfortunately there is no universal agreement about how to classify clinical types of life-threatening poliomyelitis, nor are there any generally adopted indications for the use of artificial respiration and other special measures If diagnostic criteria and indications for the different types of treatment are not clearly stated, all comparison of methods and results is futile This applies even more to another point of decisive importance the characterization of the severity of a given epidemic In these respects we are badly in need of intelligent standardization

Before a classification is attempted, attention should be called to the different competing factors playing a role in the composite clinical picture [illegible]

and lungs may be encountered In most cases one or more of these complications are present, each of them stamping its mark on the clinical picture As these rival syndromes are well known, they are only briefly outlined

arterial blood is 7.38-7.46 and for venous blood 7 34-7.43. As direct measurement of pH is not widely used in clinical laboratories, however, most clinicians rely on determinations of total carbon dioxide of the plasma in diagnosing states of alkalosis and acidosis—too low a content indicating a state of acidosis, too high, a state of alkalosis. This, in many instances, is correct, but exceptions to the general rule that the bicarbonate content and hydrogen ion concentrations in the blood move in opposite directions (that is, bicarbonate and pH vary in the same direction) are found in conditions where the acid showing an excess or deficiency is carbonic acid [70]

If direct determinations of pH with a glass electrode are done, it is very often found that total carbon dioxide is not a reliable indicator of acid-base equilibrium, as both respiratory and metabolic factors are involved in the pH actually measured, and because chemically bound CO_2 (bicarbonate) and physically dissolved CO_2 gas in the plasma, though basically interdependent, may vary seemingly independently.

It is therefore important to assess the two components determining pH—the metabolic and the respiratory. This can be done quite easily, and is, in certain cases, of decisive therapeutic importance.[2]

As in bulbar poliomyelitis—especially without vasomotor shock and concomitant kidney damage—metabolic factors do not play a conspicuous role, and as the tension of physically absorbed CO_2 in arterial blood—pCO_2—is intimately related to the CO_2 content of mixed alveolar air, and thus closely mirrors the respiratory component in a given pH, determination of pCO_2 (mmHg) is of particular value in respiratory poliomyelitis

By evaluating separately the respiratory as well as the metabolic components, a more comprehensive picture of the compensatory efforts is obtained and adequate therapeutic measures are made possible

As total carbonic acid is defined as the sum of chemically bound CO_2 (bicarbonate) and physically absorbed CO_2, these two components may be calculated from the Henderson-Hasselbalch equation after direct measurement of pH and total carbonic acid .

$$pH = 6\ 1 + \log \frac{\text{conc}\ \ HCO_3^-\ (\text{millimol})}{\text{conc}\ \ H_2CO_3\ (\text{millimol})} \quad \text{(Henderson-Hasselbalch)}$$

Plasma bicarbonate affords a supply of base which is always and everywhere immediately available for the complete neutralization of all acids Because of this, the bicarbonate of the blood has been called the *alkali reserve*, yet this is true only if referred to the normal CO_2 tension of the plasma, i.e., to a CO_2 tension of 40 mmHg.[49]

In venous blood pCO_2 is normally found to be between 40 and 53 mmHg , in arterial blood, between 35 and 45 mmHg For all practical

rising blood pressure, a relatively slow pulse, anxiety, restlessness, clouded consciousness or coma.

Vasomotor shock

This may be seen very often in some cases it is probably due to lesions of the medullary centres or myocardial damage;[15, 27, 32, 62] in others it is presumably precipitated by incorrectly administered positive-pressure ventilation, because of too high a mean intrathoracic pressure during the respiratory cycle. The clinical picture of vasomotor shock is well known: clammy extremities with mottled cyanosis, peripheral venous collapse, a feeble and rapid pulse, falling blood pressure, haemoconcentration, decreasing diuresis, and drowsiness. Yet the blood pressure is not always low because of coexisting hypercapnia, renal disease (shock kidney), or central hypertension

For obvious reasons, respiratory insufficiency in many cases is easy to diagnose, in others, with for instance only slightly reduced thoracic excursions, it may be suspected and biochemically verified, and finally there are borderline cases where it is a matter of definition whether a given case—for therapeutical reasons—should or should not be labelled respiratory insufficiency[1] Our criteria are:

(1) reduction of vital capacity to less than 50% of the calculated norm;

(2) reduction of maximum breathing capacity to less than 25%,

(3) fluoroscopically demonstrated reduction of the motility of both sides of the diaphragm or total immobility of one side;

(4) reduction of oxygen saturation below 94% and/or respiratory acidosis

Naturally these procedures cannot always all be carried out in rapidly developing cases, and if the load of patients is heavy, many patients with reduced aeration of the blood do not receive adequate therapy early enough, and some even so late that irreparable damage has been done. In a few patients reduced ventilation is due to abductor paralysis of the vocal cords, or possibly, in some cases, to adductor reflex spasm with closure of the glottis Laryngoscopy should always be done, especially if signs of pooling of secretions are present

Impairment of swallowing, with consecutive accumulation of secretions in the hypopharynx and larynx, is quite often present in bulbar poliomyelitis In some cases *it is due to actual paralysis of the muscles involved* in the process of swallowing, and is objectively demonstrable,[57] in others, pooling of secretions is due not to true muscular weakness (paralysis of the IXth, Xth and XIIth cranial nerves), but to comatose states caused

Diffuse polioencephalitis

This is characterized by slow cerebration, lethargy or coma, muscular hypotonia eventually simulating paresis, anxiety, fibrillations of the facial muscles, nystagmus or other eye symptoms, hyperpyrexia, and occasionally convulsions. Respiration is often slow, and irregular in time as well as in amplitude Paralysis of the upper cranial nerves is quite often present. Many of these patients are so drowsy that they seem to "forget" to breathe, because vigorous verbal stimulation from the doctor or nurse will often temporarily restore normal respiration, thus proving that the reduced ventilation is due neither to virus lesions of the respiratory medullary centres nor to spinal respiratory insufficiency. As soon as the patient is left alone he falls back into his semi-comatose state, and respiration again becomes shallow and irregular. In other encephalitic cases respirations are constantly of the irregular type, usually attributed to involvement of the medullary respiratory centres. Some of these patients at the same time present the picture of what is thought to be vascular centre involvement. They are dusky red, their pulse is rapid and feeble, and the blood pressure is often fluctuating. Symptoms of true focal encephalitis, with aphasia, spasticity, or convulsions, are in our experience extremely rare

The diagnosis of diffuse polioencephalitis can be made with safety only if other competing syndromes—especially hypoxia and hypercapnia—are ruled out In the 1952 epidemic polioencephalitis was quite common [56] and nearly always of primary type, the disease starting "from above", and not developing in the course of ascending poliomyelitis Late "encephalitis" symptoms are practically always due to cerebral hypoxia with or without vasomotor shock, carbon dioxide retention, hyperpyrexia, or uremia Most patients with true diffuse encephalitis have little or no peripheral paralysis, but very often accumulation of secretions in the airway hampering respiration, and quite frequently diffuse polioencephalitis, are associated with frank paralysis of the lower cranial nerves (IX-XII).

Hypoxia

In hypoxia we find air hunger, attempts at forced breathing, and a rapid pulse. The patient is restless and apprehensive, but cyanosis is usually not present before oxygen saturation comes down to 85% or lower. Oxygen deficit may cause increased permeability of the capillaries and thus enhance the danger of pulmonary oedema.

Retention of carbon dioxide (hypercapnia)

This is very common in respiratory insufficiency, insidious and dangerous. Early symptoms are : sweat, salivation, increased gastric secretion,

This classification may seem too elaborate, but we have found the different groups fairly clear-cut, and it is easy to simplify:

TABLE II. ANATOMICAL CLASSIFICATION OF BULBAR AND RESPIRATORY POLIOMYELITIS: INCIDENCE AND MORTALITY-RATES IN 345 CASES

Principal site of lesion		Cases		Case-mortality	
		number	percentage	number	percentage
A + B	Encephalo-bulbar	87	26	32	37
C	Spinal	157	45	48	30
D + E + F	Spino-bulbar-cerebral	101	29	62	61

Group A

The symptomatology of *polioencephalitis* has already been discussed. Many of these patients have paralysis of the cranial nerves, especially the upper group (nerves III-VII) and most often the facial nerve. Yet our group A includes patients with nuclear paralysis not only of the upper cranial nerves but also of the lower, as in our experience mortality is the same in encephalitic patients with or without paralysis of deglutition, and paralysis of the upper cranial nerves has no influence on mortality

Eye symptoms are very common, including all types of nuclear palsies, total ophthalmoplegia, and the various forms of nystagmus In the acute encephalitic stage it is often impossible with certainty to diagnose peripheral paralysis on account of the muscular hypotonia accompanying deep coma It is characteristic of these patients that many of them emerge quite suddenly from their comatose state, spontaneous respiration improves abruptly when consciousness and rationality return, and examination then reveals that little or no peripheral paralysis is present. Patients who survive are very often 100% cured, physically as well as mentally.[40] In 1952 the large majority of this group were children, with twice as many boys as girls

Group B

This group of *pure bulbar cases* was quite small in the Copenhagen epidemic of 1952 In groups A, D, and F there were 38, 28, and 13 cases of pharyngeal paralysis respectively

Group C

Respiratory insufficiency of pure spinal origin, without bulbar involvement, but often with heavy peripheral paralysis. In 1952 this was the

by polioencephalitis, hypoxia, or hypercapnia. In our experience only a minority of the "wet" cases have veritable paralysis of the oro-pharyngeal muscles, and the terms "pharyngeal" or "laryngeal" paralysis should be used only if actual muscular paralysis is present.

This definition, of course, is very strict and probably too rigid, as it does not include *incipient and ephemeral impairment of swallowing* In the vast majority of cases, paralysis of swallowing does not last more than one week, but we have seen cases lasting more than four months. The prognosis is good, as impairment of deglutition always clears up if the patient survives

Many patients have cerebral symptoms—here called "cerebralia"—probably not due to virus infection of the brain In such cases apathy or coma is not primary, i e., not initial, as in typical polioencephalitis. Arbitrarily, we have used the term "cerebralia" in our classification of patients only where such cerebral symptoms were present for more than two days They are due to anoxia and its sequels, hypercapnia, hyperpyrexia, and uremia All these patients had severe peripheral paralysis, in contradistinction to those with true polioencephalitis.

TABLE I. CLINICAL CLASSIFICATION OF BULBAR AND RESPIRATORY POLIOMYELITIS. INCIDENCE AND MORTALITY RATES IN 345 CASES

	Clinical groups	Principal site of anatomical lesion	Cases		Case-mortality	
			number	per-centage	number	per-centage
A	Polioencephalitis	encephalo-bulbar	75	22	29	39
B	Pharyngeal and/or laryngeal paralysis, without encephalitis or cerebralia, no peripheral paralysis	bulbar	12	4	3	25
C	Paralysis of spinal respiratory muscles, without encephalitis, cerebralia, or pharyngeal paralysis	spinal	157	45	48	30
D	*Paralysis of spinal respiratory* muscles and of pharynx or larynx, without encephalitis or cerebralia	spino-bulbar	28	8	13	46
E	Paralysis of spinal respiratory muscles, with cerebralia, but without true pharyngeal paralysis	spino-(bulbar)-cerebral	60	17	38	63
F.	Paralysis of spinal respiratory muscles and of pharynx or larynx, and with cerebralia	spino-bulbar-cerebral	13	4	11	85
	Totals		345	100	142	41

TABLE III. SURVEY OF 345 PATIENTS WITH LIFE-THREATENING POLIOMYELITIS

Patients			Deaths		
condition	number		number *		percentage
With impairment of deglutition but without respiratory insufficiency	12		3		(25)
With respiratory insufficiency	333		139		42
With respiratory insufficiency and artificial respiration	262	333	122	139	47
With slight respiratory insufficiency, no artificial respiration	71		17		24
With artificial respiration and tracheotomy	236	262	107	122	45
With artificial respiration, no tracheotomy	26		15		58
"Wet" cases with pooling of secretions in pharynx and respiratory tract, all with reduced ventilation	228	333	102	139	45
"Dry" cases without pooling of secretions in pharynx and respiratory tract, all with reduced ventilation	105		37		35
"Wet" cases having a tracheotomy	198	228 / 333	87	102 / 139	44
"Wet" cases, no tracheotomy	30		15		50
"Dry" cases having a tracheotomy	69	105	25	37	36
"Dry" cases, no tracheotomy	36		12		33

* A total of 142 fatal cases

TABLE IV. "WET" CASES IN RELATION TO LOCALIZATION OF SECRETIONS

Number			Deaths		
			number		percentage
Secretions in trachea, bronchi, and lungs	97	228	55	102	57
Secretions only in pharynx and larynx	131		47		36

TABLE V. "WET" CASES WITH A TRACHEOTOMY IN RELATION TO LOCALIZATION OF SECRETIONS

Number			Deaths		
			number		percentage
Secretions in trachea, bronchi, and lungs	86	198	46	87	53
Secretions only in pharynx and larynx	112		41		37

Here the principle of classification is based on the most important clinical symptoms—respiratory insufficiency and the state of the airway.

largest group, and no less than 80% had paralysis—generally severe—of the upper extremities.

Group D

Paralysis of respiratory muscles and pharyngeal or laryngeal paralysis without cerebral symptoms, i e., patients with *true bulbo-spinal poliomyelitis*

Group E

Paralysis of respiratory muscles and "cerebralia", but without true paralysis of pharyngeal muscles.

Group F

Paralysis of respiratory, pharyngeal and/or laryngeal muscles, and "*cerebralia*"

Groups E and F are nearly identical, and in these we find the most severe cases. In 1952 they comprised 73 patients, of whom 86% had bilateral paralysis of the arms, often of extreme severity.

It will be noted that we have omitted a special autonomic centres group. This is not because symptoms usually attributed to involvement of the respiratory and vasomotor centres in the reticular formation were never encountered They no doubt were, but never in a pure, isolated state, and, because of co-existing complications, rarely so clear-cut that the diagnosis could be made with safety In 1952 we did see a certain number of patients in the groups A, B, E, and F who were dusky-red, with irregular shallow respiration despite strong respiratory muscles, periods of Cheyne-Stokes respiration, and vasomotor instability. Undoubtedly many of our numerous patients with the clinical picture of primary vasomotor shock had involvement of the medullary centres. They practically all died, and all showed extensive lesions in their reticular formation.

The anatomico-clinical classification given in table II has the advantage of following the conventional lines[3, 4, 13, 22, 31, 41, 42 69] of grouping patients with bulbar and respiratory poliomyelitis, and our material can thus be compared with other data, but it does not take into account the all-important question of specific treatment indications, and has no relation to the fact that life-threatening poliomyelitis is mainly and foremost a problem of oxygenation and elimination of carbon dioxide—a problem of maintaining an unobstructed airway.

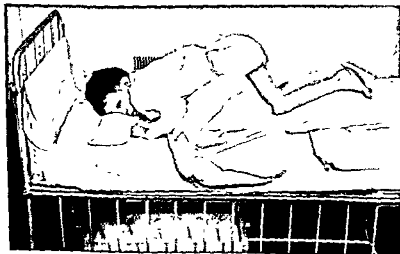
In tables III, IV, and V a classification is presented based on the therapeutically decisive clinical symptoms and the treatment instituted during the Copenhagen epidemic of 1952

harmful and often life-saving In many clinics such patients with incipient respiratory failure are given a period of respirator treatment both to get the patient accustomed to the machine and to rest his muscles[52] It is psychologically important that the respirator is not used as an ultimum refugium, but I am not sure that a real rest of the respiratory muscles can be achieved

If there is only slight or moderate accumulation of secretions in the upper airway, with no, or only little, reduction of ventilation, the patient should be placed in the postural drainage position, eventually combined with intermittent or continuous suction of the hypopharynx and larynx. As many patients of this type have gastric distention, an in-dwelling stomach-tube should always be inserted, and the stomach kept empty in order to avoid spilling-over or vomiting of acid gastric contents, with aspiration into the airway As most adult patients do not tolerate being in a Trendelenburg position of 30°-40° for more than very short periods of time, and such a position is unsuitable hydrostatically, the supine position should be abandoned whenever possible and the patient placed in a semi-prone position, which is just as effective with an inclination of only 10°-20° The best position in which to place the patient is with the pelvis high and *the head and feet low (see fig 1 and 2)*

If by these measures, supplemented by lung physiotherapy, adequate ventilation is not restored, the patient should immediately be placed in a respirator capable of producing adequate volumes of tidal air The setting

FIG 1. IMPROVISATION OF POSTURAL DRAINAGE



The survey indicates the treatment actually instituted in these circumstances, under the enormous load of patients urgently requiring life-saving measures, under the stress of improvisation, rigging-up new equipment, instructing the ever-increasing staff of untrained personnel, and with hopelessly inadequate supplies of mechanical means of giving artificial respiration at the onset. It was thus not always possible strictly to follow the ideal treatment-indications, and the figures therefore do not express what we would have done under circumstances less strained.

OBSERVATION PERIOD

Any patient with acute poliomyelitis may develop life-threatening symptoms. Yet such symptoms usually start quite early, during the first few days of the meningitic phase, and respiratory and bulbo-encephalitic symptoms are especially to be expected in patients with high fever, clouded consciousness, muscular twitchings, ascending paralysis, or paralysis beginning in the upper extremities. In these last-mentioned cases respiratory difficulty is the rule. As hypoxia, aspiration of secretions, and hypercapnia may develop extremely rapidly, observation by trained personnel is imperative, as a patient may choke to death in the course of a few minutes. This means that patients with high fever, apprehensiveness, twitchings, clouded consciousness, feeble cough, reduced respiratory excursions, etc., must be supervised unremittingly in order to avoid deleterious episodes of hypoxia and hypercapnia. The temperature should be taken frequently, the blood pressure, pulse, and respirations charted hourly, the vital capacity or maximum breathing capacity measured at short intervals, and bed-side x-rays of the lungs and fluoroscopy of the diaphragm done if possible. The progression of peripheral paralysis should be watched closely without exhausting the patient, and special emphasis should be placed on the appearance of paralysis of the upper extremities and neck muscles. Can the patient cough? Can he swallow? Does inspection of the pharynx and larynx reveal muscular paralysis or pooling of secretions? How is the voice? Are the lungs clear? Are the respiratory excursions reduced on one side or on both sides? Is respiration paradoxial, as in paralysis of the diaphragm? Does the patient use the auxiliary respiratory muscles? How is his mental state? And finally—finally, because action should be taken before—is the patient dyspnoeic or cyanotic? If in doubt, oxygen saturation and carbon dioxide tension should be measured.

As hypoxia and hypercapnia are harmful to the nerve cells and should be avoided at all costs,[58] many clinicians are in favour of early intervention,[13, 23, 25, 69] which, no doubt, is a sound policy, and the more so because early—or in certain cases even prophylactic—therapy is presumably never

much spontaneous respiration that further mechanical aid is unnecessary. Others can then be placed in tank or cuirass respirators; but in our experience intratracheal positive-pressure ventilation—manual or mechanical—is often far more efficient because of far better observation facilities. Patients with respiratory insufficiency and a free airway—the "dry" cases—are good subjects for treatment in tank respirators, and in cuirass respirators if their spontaneous ventilation is not too low They also, however, can be ventilated by positive-pressure methods—manual or mechanical

During the epidemic of 1952 the final treatment of 208 patients was tracheotomy and positive-pressure ventilation from a bag In 60% of the group this was the initial treatment, but 57 had first been subjected to postural drainage and repeated suctions of the hypopharynx, and 30 furthermore had been in a respirator—cuirass or tank In two-thirds of the patients originally placed in the postural drainage position, we had to resort to tracheotomy because of persisting obstruction, and three-fourths of the patients originally placed in respirators had to have tracheotomies.

TRACHEOTOMY

Indications for Performance

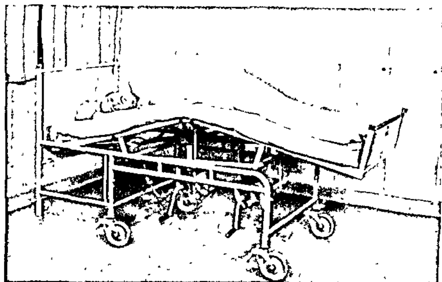
Tracheotomy in bulbar and respiratory poliomyelitis was first introduced in 1932[54] Since then, and especially after Galloway's work,[23, 24 25] the pros and cons for the operation have been widely discussed[29, 45] The general tendency now seems to favour early, if not prophylactic, tracheotomy[39] In our opinion the advantages far outweigh the disadvantages, which are negligible Tracheotomy is not a mutilating operation, but, naturally, it is one which should not be lightly performed, it should always be based on sound clinical judgement, taking into account all practical circumstances (equipment, nursing facilities, transportation, etc)

The main indication for tracheotomy is obstruction of the airway with reduced ventilation that cannot be relieved by postural drainage and intermittent or continuous suctioning It should be performed.

(1) in patients admitted in a state of hypoxia, cyanosis, restlessness, or coma, with obstruction of the airway by secretions or gastric contents; here tracheotomy is life-saving, and should be done without delay (*vital indication*),

(2) in *polioencephalitis* with coma, extinguished reflexes, secretional obstruction, and hypoventilation, especially when restlessness makes postural drainage impracticable and suctioning inefficient,

FIG. 2. POSTURAL DRAINAGE BED (C. G. ENGSTRÖM)



of the respirator should aim at securing normal ventilation, and hyperventilation with respiratory alkalosis should be avoided In this way a certain number of patients can be tided over the acute, life-threatening phase of the disease, especially in modern tank respirators where a position of postural drainage can be maintained In the majority of cases with pooling of secretions and impairment of deglutition, however, proper ventilation cannot be kept up in this way, because the respirator—as would any type of ventilation—will tend to suck secretions farther down into the airway during the inspiratory phase in patients with defective ciliary function and extinguished cough reflex, plugging and atelectasis ensue, resulting in unsatisfactory alveolar ventilation

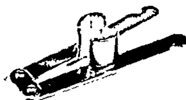
It is a universal experience that the conventional respirator is contraindicated in most " wet " cases, because of the impossibility of maintaining an unobstructed airway [68] Therefore, the moment it is clear that the airway cannot be kept sufficiently open in a respirator known with certainty to produce adequate volumes of tidal air, and in spite of postural drainage and frequent intermittent suction, a high tracheotomy should be done, with insertion of the widest possible metal or rubber tube with an inflatable cuff in order to seal off the airway so that aspiration of secretions and gastric contents is made impossible.[13] We consider the cuff-tube very important; suction can be performed much more effectively through the tube than through the nose or mouth, and bronchoscopy is much easier to perform. After tracheotomy some " wet " patients immediately regain so

slide down beyond the carina (see fig. 3 and 4)

If the tube is too long or slides down it will nearly always find its way into the right main bronchus, causing hypoventilation and eventually atelectasis of the left lung

The tracheal tube should be changed quite often in cases with abundant secretions; in others it can be left in place for days or even weeks if cleaned frequently

FIG. 4. CLOSE-UP OF DEVICE TO KEEP RUBBER CUFF-TUBE IN PLACE



The cuff-tube should be replaced by an ordinary silver canula as soon as swallowing is restored and the danger of aspiration from above eliminated Positive-pressure ventilation proved to be very effective even in patients with an ordinary silver canula, where the leak naturally is considerable. Decanulation should not be attempted before swallowing is normal and the patient can cough and keep his airway free of secretions Some of these patients go directly from positive-pressure ventilation, manual or mechanical, to spontaneous respiration, in others, respirators of the tank or cuirass type, or the rocking bed, must be resorted to for varying periods of time

If there is pronounced bilateral weakness of the diaphragm, or if one side is heavily paralysed, atelectasis will often appear when decanulation is attempted, in spite of vigorous coughing and breathing exercises and tapotement.

On the whole, atelectasis is very common in the acute patient with reduced ventilation, no cough reflex, and accumulation of secretions in the bronchial tree Three-fourths of our 270 patients with a tracheotomy had atelectasis at one time or another, often easy to diagnose clinically because, in patients with intratracheal positive-pressure ventilation, inspection of the thoracic excursions is easy, and stethoscopy and bedside x-ray can be done, whereas patients in a cuirass or, especially, in a tank respirator, cannot be observed by any means as closely In about 40% atelectasis could be overcome by suction through the tracheal tube or directly through the opening in the trachea, in the remaining 60% it cleared up after bron-

physiotherapists

(3) in *bulbar* cases with paralysis of the lower cranial nerves and accumulation of secretions in the airway, resulting in atelectasis in spite of mechanical aspiration and postural drainage;

(4) in *bulbo-spinal* cases where the airway cannot be kept open;

(5) in other cases of reduced ventilation requiring artificial respiration where adequate mechanical equipment is not available

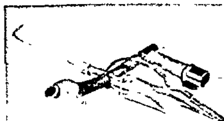
We have practically never regretted doing an early tracheotomy, but have several times deplored that the operation was done too late. Yet, certain complications after tracheotomy are encountered—for example: (1) difficult decanulation—which is quite common, (2) infection—which is prolonged by the irritation caused by the endotracheal tube, and (3) mediastinal emphysema and pneumothorax—which, in our experience, is very rare

Surgical Technique

The first step of the operation is tracheal intubation through the mouth, thereby securing effective aspiration from the upper airway during the surgical intervention, and adequate insufflation of oxygen and anaesthetic In our cases we have always used general anaesthesia with cyclopropane.[13] If this anaesthetic is not at hand, ether can be recommended Intravenous barbiturates should never be given as an anaesthetic, and sedatives should not be used, even in irrational and apprehensive patients, before adequate ventilation is secured After this has been established, sedatives may be beneficial, in some cases even curare has been recommended [20, 21, 47]

The operation is done at the highest possible level, with excision of an oval opening in the trachea If time permits, a suction catheter is introduced into the trachea and the main bronchi, and aspiration is begun under intermittent manual squeezing and pressing of the thorax to loosen secretions causing plugging and atelectasis of the lungs. After this a rubber or silver cuff-tube is inserted and the cuff inflated to prevent aspiration of secretions from above. At the same time the intubation tube is withdrawn It is important to use a cuff-tube with the widest possible inner diameter and to secure the tube so that it does not

FIG. 3. ENDOTRACHEAL RUBBER TUBE WITH CUFF INFLATED, AND DEVICE TO KEEP TUBE IN PLACE



patients the cause is often inadequate pressure settings of the machine. If frank symptoms of hypoxia and hypercapnia are not present but hypoventilation is still suspected, determinations of tidal flow per minute, or of oxygen saturation and CO_2 tension, should be made, after aspiration of secretions has been tried and respirator settings adjusted Hypoventilation should be considered in terms of carbon dioxide tension as well as oxygen saturation.

(4) *Hyperventilation* spontaneous hyperventilation is the rule in acutely ill, febrile patients, and thus, also, in acute poliomyelitis It is even—for reasons not quite understood—very common in incipient, yet evident, respiratory distress Hyperventilatory efforts are without doubt tiring for the weakened respiratory muscles

Furthermore, all types of mechanical respiratory aid tend towards a state of hyperventilation, i e, subnormal tension of CO_2 This happens partly for psychological reasons—because, for example, the medical personnel setting the respirator pressures naturally want to avoid hypoventilation and consequently are apt to supply the patient with air too generously—and partly because tidal volumes securing adequate oxygenation may at the same time cause excessive elimination of carbon dioxide (low pCO_2). Most often the ensuing respiratory alkalosis is only moderate and presumably harmless, though weaning from the respirator is more difficult, probably because the respiratory centre becomes accustomed to abnormally low CO_2 tensions In more pronounced respiratory alkalosis, ionized calcium in the serum may decrease so that tetany develops. This only rarely occurs, but prolonged respiratory alkalosis no doubt plays a role in the pathogenesis of renal calculi, which are quite often seen in chronic respirator patients

(5) *Vasomotor shock* is extremely common in acute encephalitic and bulbar poliomyelitis In some cases it is caused by lesions of the vasomotor centres, in others precipitated by hypoxia, hypercapnia, or myocardial damage [15, 32 62] Finally, quite a few cases seem to be caused by incorrectly administered mechanical—or manual—artificial respiration If the mean intrapulmonary pressure is too high during the respiratory cycle, venous return to the right heart will be hampered, resulting in lowered cardiac output, peripheral circulatory collapse with hypotension, haemoconcentration, and shock Pressure curves should be adjusted and early cautious anti-shock therapy instituted

(6) *Pulmonary oedema is not a rare complication* When present it is an ill omen and spells a very bad prognosis, nearly always fatal Its pathogenesis is complex suddenly released bronchial stop, hypoxia with changes of capillary permeability, myocardial damage, especially of the left side, and involvement of the medullary vasomotor centres, and in certain cases

COMPLICATIONS
IN BULBAR AND RESPIRATORY POLIOMYELITIS

In acute patients with impairment of swallowing or reduced ventilation, or with both, complications are many, frequent, and often life-threatening, especially when they interfere with the free passage of air. A few minutes of obstruction may prove fatal. Patients of this type—especially the "wet" cases—should therefore be under continuous supervision, not solely by a trained nurse, nor by some young doctor just out of medical school, but by a physician thoroughly familiar with all the complications which may arise, capable of coping with any emergency situation, and able to act quickly and resolutely, otherwise lives are lost.

The only rational solution of this problem is the creation of poliomyelitis centres specifically adapted and staffed for the treatment of life-threatening poliomyelitis In the Copenhagen epidemic, teams were set up comprising physicians especially familiar with poliomyelitis, anaesthetists, otologists, laboratory specialists, physiotherapists, and specially trained nurses

(1) *Bacterial infection* of the bronchial tree and lungs is extremely common, and so are its sequels of incrustations, bronchitis, pneumonitis, and atelectasis This can to some extent be counteracted by securing 100% humidification of the inspired air at body temperature, instillation of [illegible] of bicarbonate, and antibiotic therapy. However, even

specific resistance of each strain to the commonly used antibiotics, therapeutic results are often discouraging. After some time the strains will become resistant to all known antibiotics If many patients are together, their bacterial flora tend to become identical, and the infection becomes established as nosocomial In our experience such intractable infection is always overcome if the patient regains sufficient spontaneous respiration to become independent of mechanical aid, and if the tracheotomy wound can be closed

(2) *Atelectasis* is accompanied by fever, reduced ventilation, often resistance to the free passage of air, asymmetric movements of the thorax with lagging behind of the affected side, dullness and inaudible breath sounds, and x-ray changes. The attending personnel should constantly be on the look-out for atelectasis, which should be treated promptly by postural drainage, suctioning, bronchoscopy, and physical lung therapy.

(3) *Hypoventilation* may be due to weakness of the respiratory muscles, infection, and accumulation of secretions with atelectasis. In respirator

(12) *Haemorrhagic diathesis* with manifest bleeding is frequently seen in patients who have gone through hypoxic episodes, and is most often due to increased capillary permeability A low prothrombine content is rare, but is easily remedied by injections of vitamin K.

Other complications are hypochromic anaemia, renal calculi, phlebitis, and bed-sores They are usually of no prognostic significance

In table VI the incidence of certain complications in 345 cases of life-threatening poliomyelitis is presented, together with the corresponding mortality-rates

TABLE VI. MORTALITY-RATES AND FREQUENCY OF COMPLICATIONS IN 345 PATIENTS WITH IMPAIRMENT OF DEGLUTITION AND/OR RESPIRATORY INSUFFICIENCY

Complication	Frequency		Lethality	
	number	percentage	number	percentage
Shock	134	39	90	67
Paralytic ileus	114	33	49	43
Hyperpyrexia	66	19	60	91
Hypertension	65	19	27	42
Azotemia	36	22	28	78
Pulmonary oedema	28	8	26	93

This table shows that vasomotor shock and paralytic ileus were very common, while azotemia and pulmonary oedema occurred in only about 10% of cases with bulbar and respiratory poliomyelitis Patients with hypertension and paralytic ileus had the same chance of survival as the whole group, whereas vasomotor shock, azotemia, hyperpyrexia, and pulmonary oedema were, in the order mentioned, of increasingly ominous prognostic significance. Nearly all patients with hyperpyrexia or pulmonary oedema died

MECHANICAL RESPIRATION

Body and Cuirass Respirators

No mechanical respirator can produce physiological respiration, in respect either to intrathoracic pressure curves or to circulatory effect. Most respirators now in use are far from ideal, but recent studies, mostly in the USA, of the ventilatory and circulatory characteristics of the different types have done much to increase our understanding of the underlying problems and have led to rational improvements [8, 59, 64, 65, 66] As these are

overdosage of fluids and sodium chloride.[60] Therapy should be prompt and radical, but is, in our experience, most often ineffective.

(7) *Azotemia* with increased non-protein nitrogen is present in nearly all bulbar patients, and is due to disintegration of the paralytic muscles, inanition, and kidney damage caused by vasomotor shock. If true uraemia with low diuresis is present the usual anti-uraemic treatment is indicated, but uraemia is prognostically of very grave significance.

(8) *Hyperpyrexia* is common in the acute stage, particularly in patients with polioencephalitis In such cases it is probably of "central" origin; in others it is due to secondary infection of the lungs. Antipyretics and antibiotics are usually ineffective, but cooling (wet blankets) or intravenous injections of alcohol, causing dilatation of the capillaries of the skin, are occasionally of some benefit. The prognosis is very grave.

(9) *Paralytic ileus* with atonia of the stomach is, in our experience, one of the most common complications in bulbar poliomyelitis In some cases it is probably caused by virus damage to the vegetative centres, in others by shock or low serum potassium These patients are in grave danger of vomiting followed by aspiration of gastric contents into the airway. Furthermore, the movements of the diaphragm are hampered because of the high intra-abdominal pressure, and postural drainage is difficult. Treatment consists in · permanent stomach-tube with constant suctioning, prostigmine, high enemas, and maintenance of a normal fluid and electrolyte balance (potassium)

(10) *Hypertension* is extremely common in patients with bulbar and respiratory poliomyelitis. In most cases—generally transient—it is due to hypoventilation with hypercapnia and is often easily adjusted. In a few cases, hypertension is persistent without relation to hypercapnia and may reach high degrees with systolic pressures of up to 240-280 mmHg and diastolic pressures of up to 140-160 mmHg. This type, which may be reversible, with reversible changes of the eye-grounds, is probably due to central virus lesions It is very seldom seen in non-paralytic cases, somewhat more often in cases with peripheral paralysis, and most often—though still infrequently—in bulbar and encephalitic cases [11] In many cases of vasomotor shock the blood pressure is normal or increased, usually because of hypercapnia, in a few instances due to "central" hypertension.

(11) *Paralysis of the bladder* with retention of urine is by no means rare An in-dwelling catheter is often necessary for a few days, but urinary retention rarely persists for more than one or two weeks. Infection of the urinary tract may become established, however, and should be treated along the usual lines after isolation of the causative organism and after testing its sensitivity to the ordinary antibiotics. Persistent urinary infection no doubt plays a role in the formation of renal calculi

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FIG. 5. TANK-RESPIRATOR (DRAEGER) WITH DOME ATTACHED

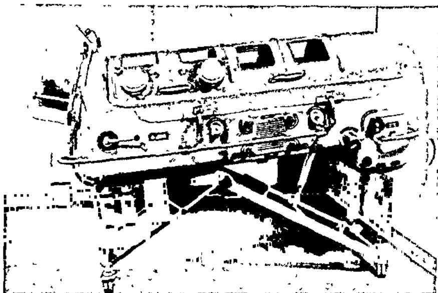
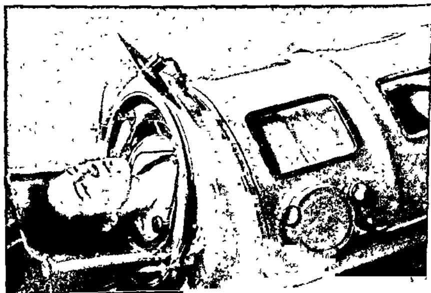


FIG. 6 TANK-RESPIRATOR (DRAEGER) SHOWING NECK-CLOSURE PERMITTING TRACHEOTOMY



quite recent, nearly all respirators now in use are old-fashioned and far from optimal. Yet they seem to be quite effective in most cases where they are used, producing adequate ventilation and no noticeable harm to the circulation This, at least, is true in patients past the acute phase of respiratory insufficiency, and in chronic cases, who seem to be able to adapt the circulation to unphysiological pressure conditions in the thorax In the acute, "wet" patient with circulatory instability or vasomotor shock and reduced cardiac output this adaptation, with restoration of a normal venous gradient, does not seem to be possible,[10, 63] and this is probably a contributory reason why the conventional respirators so often fail in the acute stage The main reason is, of course, that the machine cannot produce adequate ventilation when the bronchi and lungs are full of secretions

A mechanical respirator must first of all be capable of offering the patient an adequate amount of air or oxygen from six to ten litres per minute. The intrapulmonary pressure-curve must be of the type causing the least possible resistance to the venous return to the right heart, in order to avoid shock and decreasing cardiac output [10, 37, 35, 63] Finally the respirator must be so constructed mechanically that it can keep going for weeks or months with a minimum of attention from the nursing staff In fact, it should be foolproof

In order to fulfil the basic ventilatory and circulatory demands, the pressure-curve delivered by a respirator should not be a half sinus-wave-curve, where inspiration and expiration are of equal lengths and the minimum intrathoracic pressure never lower than the ambient pressure.[8] Sinus wave curves are produced in all conventional crank-actuated tank or cuirass respirators and in most machines used for intratracheal positive-pressure ventilation. The inspiratory peak should be rather high and sharp, corresponding maximally to 20-30 cm of water It should be high enough to deliver an adequate volume of tidal air, but not so steep that the pressure is inconvenient for the patient The inspiratory phase should cover not more than one-third of the whole respiratory cycle and should end by a sharp expiratory release, bringing the pressure down to ambient pressure, usually atmospheric, or slightly below, coming back to base-line during the expiratory pause, which should be respected If positive expiratory intra-tank pressure is produced, the inspiratory peak pressure may be reduced while still securing adequate tidal flow in spite of decreasing mean intrathoracic pressure during the respiratory cycle The lower this mean pressure is, the less is the depressive effect on the venous return to the right heart, on the cardiac output, and on the blood pressure [10, 37, 38, 63]

Tank respirators

In most tank respirators rhythmic negative intra-tank pressures make the chest expand, with resulting inspiration Expiration is passive, the

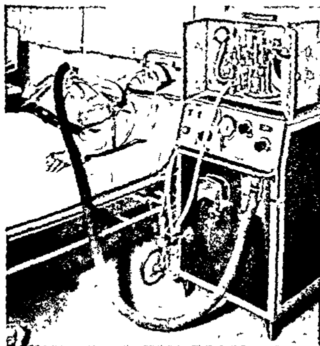
pressure returning to zero, i e , atmospheric pressure. Yet in modern tank respirators it is possible to assist expiration actively through positive intra-tank pressures On account of the fact that inspiration is actuated by negative intra-tank pressures, most people do not seem to realize that the body respirator really works as a positive-pressure breathing machine just as do machines designed for intratracheal positive-pressure ventilation. This is due to the fact that when a vacuum appears to perform work—as in the tank respirator—the work is in reality done by the relatively positive reference pressure, i e., atmospheric pressure [38] It is simply a question of base-lines In machines producing intratracheal positive-pressure ventilation, the base-line is atmospheric pressure, 760 mmHg, but in a body respirator working at a negative inspiratory pressure of − 20 mmHg the base-line is 740 mmHg In cuirass respirators, especially those not encircling the body, conditions are more complicated, yet these, too, are mainly positive-pressure machines

The tank respirator was first introduced in 1929 [16, 17, 18, 44 55] Until recently it had undergone very little change. The usual crank-actuated body respirator produces a sinus wave pressure-curve with inspiratory negative intra-tank pressures up to − 20 cm of water, coming back to zero during expiration. Positive intra-tank pressures during expiration, in combination with a lower inspiratory negative "pressure", often seem to produce higher volumes of tidal air Thus a setting of from + 10 to − 10 is usually more satisfactory than − 20 to 0 cm of water.[64] If the airway is unobstructed and the tank does not leak, most tank respirators will produce adequate ventilation if properly handled—and they are very easy to handle. This, together with great reliability, is their big advantage. Modern tank respirators, like the one developed by Bennet [8] and others (Drinker, Emerson, Draeger), are so constructed (see fig 5) that intermittent positive-pressure ventilation may be administered by enclosing the head in an air-tight dome, so that the tank can be opened for injections and nursing purposes By using a specially designed rubber collar, it is possible to have tracheotomized patients in these tanks (see fig 6), and by synchronizing a small cam-actuated bellows to the movements of the tank it is now possible [8] to give intratracheal positive-pressure ventilation to a patient in a tank This is said to be a great advantage in acute patients, and probably is, especially if suction is applied to the expiratory phase

The disadvantages of body respirators are obvious. First of all, there is the psychological effect. The patient is encased in a metal box—the dreaded " iron lung "—shut off from the outer world. Even if he has no peripheral paralysis, he cannot move, and, if paralysed, his extremities cannot be placed so as to prevent contractures. He is difficult to nurse, to be given injections or the bed-pan, and physical treatment of the peripheral paralysis nearly always present must be abandoned. If the patient has

hyperpyrexia, or if the outside temperature is high, he cannot be cooled down Changing of position in order to avoid congestion or atelectasis of the lungs is often not possible, or possible merely to a very limited degree, as only the most modern tank respirators allow of effective tilting No body respirator I know of permits of either efficient postural drainage or placing the patient in the prone position Finally, the price of a modern body respirator is high ($4,000)

FIG. 7. THE KIFA CUIRASS RESPIRATOR WITH GULLBERG ATTACHMENT



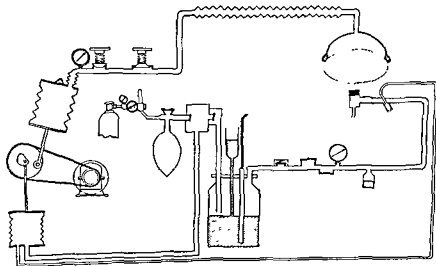
During the Copenhagen epidemic in 1952, 51 patients with respiratory failure were started in tank or cuirass respirators because we hoped that they might be tided over in this type of respirator In 39 of these cases we had to resort to tracheotomy and manual positive-pressure breathing—bag ventilation—and only 12 patients could be continuously ventilated in tank or cuirass respirators till spontaneous respiration returned This, of course, was due to the fact that only very few patients of that epidemic were really well-suited for treatment in a tank, and as a whole the tank respirator

is only rarely effective in bulbar poliomyelitis The ideal case for this treatment is the patient with pure spinal respiratory insufficiency without bulbar involvement, i e , without accumulation of secretions in the airway —the one who remains " dry ". In certain epidemics this type appears to be quite common

Cuirass respirators

In cuirass *respirators negative pressure is produced rhythmically* inside a light metal or plastic shell, thus creating inspiration. By releasing suction, expiration follows passively through the elastic recoil of the thorax, or it may be assisted by *alternate low positive pressures.* The most commonly used types of cuirass respirators are Swedish or American—Sahlin, Kifa (see fig 7), Monaghan. They are usually applied to the anterior surface of the body from the sternal notch *down to the anterior spine of the* ilium As the thoracic cage is rather stiff, these respirators probably exert most of their effect through sucking out the anterior abdominal wall during the negative intra-shell phase, thus moving the diaphragm downwards [50] Often it is not easy to make them sufficiently airtight to keep up negative pressures. This is particularly true of the old-fashioned Sahlin type, despite the fact that the patient is strapped down so tightly that he cannot move Friction sores, therefore, are rather common In the Kifa the shell is so

FIG. 8. DIAGRAM OF KIFA CUIRASS RESPIRATOR WITH SYNCHRONIZED GULLBERG ATTACHMENT FOR ENDOTRACHEAL POSITIVE-PRESSURE VENTILATION



pliable that it is easy to adapt to the body of the patient. Its great advantage is the inflatable rubber tube attached to the edge which, by suction, seals off the shell (see fig 8) The Kifa does not require much experience to handle. Furthermore, the machine is remarkably dependable. The patient may be in a semi-reclining position or may even sit up, which naturally is a great advantage. Nursing and treatment of the patient in the Kifa are easy, postural drainage in the supine position is possible, and patients do not seem to be afraid of these machines. Yet cuirass respirators have some disadvantages which limit their use considerably In patients with greatly reduced vital capacities they often do not produce sufficient ventilation, and, like the body respirators—and for the same reasons—they are only rarely effective in " wet " cases Their domain is the " dry " case with spinal respiratory insufficiency and some spontaneous respiration. Cuirass respirators are particularly useful in the weaning period.

The price is about $2,000.

Positive-Pressure Ventilation

Prolonged intratracheal positive-pressure ventilation has hitherto been used very little in the treatment of poliomyelitis with respiratory insufficiency, for two reasons: the procedure was thought to be too unphysiological for prolonged use, and people were for some reason reluctant to abandon the idea of the "iron lung" as the only means of ventilating patients with severe respiratory failure

In our case, in 1952, manual bag ventilation was introduced as an emergency measure, because of the catastrophic situation for which only a few mechanical respirators were available. Tracheotomy and positive-pressure ventilation were, in the circumstances, the only means of treating the great number of patients with bulbar and respiratory disease Time has shown that intratracheal positive-pressure ventilation—manual or mechanical—can be kept up continuously for at least two years Even though intermittent positive-pressure breathing may be said to be unphysiological, Drinker has called it the best line of attack for the promptest possible restoration of normal respiratory movements [43] Several workers [12, 43, 63] have tested the mechanical features of different types of positive-

the circulation in normal patients, but the slight effect observed was proportional to the height of the mean mask-pressure The suck-and-blow machine did not produce adverse effects on the circulation when used for one hour on two patients in deep coma The others had only a slight to

moderate depressive effect. However, from other work [10, 37, 38] it appears that if there is instability of the circulation, intermittent positive-pressure breathing regularly produces decreasing cardiac output, and the more so the higher the mean pressure during the respiratory cycle. On theoretical grounds this appears quite plausible, and for the same reasons suction during expiration is probably valuable in increasing venous return.

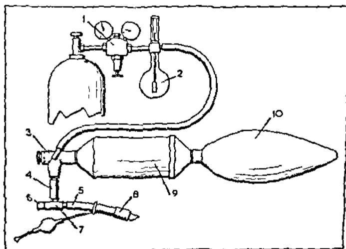
Manual bag ventilation

In fig 9 are shown schematically the various parts of the simple equipment we used with about 300 patients subjected to manual bag ventilation [33, 34, 35] The upper part of the cuff-tube has a side branch connected with a metal container packed [illegible]

[illegible]

tion of the pressure in the system. The cuff-tube is closed with a rubber stopper. If aspiration is needed, the stopper is removed and a Tiemann's catheter is introduced, mounted on a jet suctioning apparatus. We have mostly used the ejector effect of a cylinder of compressed air, which is very effective and independent of electric power A good humidifier is essential, especially when the absorber is replaced by a non-return valve (see page 187).

FIG. 9. EQUIPMENT FOR BAG VENTILATION WITH CO_2 ABSORBER AND RUBBER CUFF-TUBE



1. Reduction valve, 2 humidifier, 3 reduction valve, 4. connexion, 5 rubber tube, 6 rubber stopper, 7 connexion, 8 cuff-tube; 9 absorber, 10. rubber bag

The canister should be filled evenly with granulated soda lime of the best available quality, to avoid insufflation of particles of soda lime into the upper airway, causing irritation and increased secretion The canister must therefore be aired thoroughly by blowing a strong current of air through the container before it is used We found American soda lime (Wilson) the most suitable for the purpose Unfortunately, it is rather expensive, costing about $4 daily for each patient

FIG. 10 BAG VENTILATION WITH ABSORBER



If the precautions mentioned are followed, no ill effects are observed. It is necessary to have two canisters for each patient, and to change them every half-hour After five hours' use the contents must be changed

As will be seen from fig 9, it is a closed to-and-fro system similar to the one used in modern machines for general anaesthesia, where carbon

dioxide is effectively removed and an adequate supply of oxygen secured when the flow-meter registers 5-10 litres per minute. The bag is compressed from 16 to 30 times per minute, according to the patient's condition and age. The amount of oxygen mixture that should be given at each compression of the bag depends on the thoracic excursions and the general condition of the patient. The insufflation pressure must be short, and released completely during expiration. This is very important for reasons already explained At all times the bag should be only partly full of gas (see fig 10) This can be regulated through the flow-meter and the valve at the top of the canister We have several times measured the insufflation pressure when bag ventilation is administered correctly. It amounts to 20-30 cm of water The insufflation phase, however, must be short

Bag ventilation is especially well suited for emergency treatment of patients where modern equipment for mechanical respiration is not available, and particularly before and during transportation by car or by aeroplane to a treatment centre It is independent of electric power.

The method has great psychological advantages The patient is not encased in a cask, the notorious "iron lung", with its collar either too tight, or too loose to maintain the necessary intra-tank pressures There is no danger of friction sores, which are so common when the cuirass respirator is used All the members of the staff and the many visiting colleagues have been greatly impressed by the look of our patients receiving bag ventilation, by their calm, their apparent confidence, and total lack of apprehensiveness The beneficial psychological influence of the person assisting the patient is often very great; it helps to keep up morale, creating confidence because the patient feels that somebody he knows well is always there, ready to help This psychological assistance is especially important when the patient is regaining spontaneous respiration, and shortens the often difficult weaning period

The method has certain obvious disadvantages -

(1) Particles of soda lime may be carried down into the bronchi and alveoli.

(2) The assistance of well-trained personnel all round the clock is essential and costly

Provided the best available preparation of soda lime is used, and the canister is packed carefully and thoroughly aired before being used, the danger that particles may be carried down into the lungs seems to be more theoretical than practical Nevertheless, the desirability of completely avoiding the use of absorbers is evident, and consequently we have experimented with different kinds of valves separating the ingoing and outgoing flow of air, and at the same time securing atmospheric pressure in the lungs

during the major part of the respiratory cycle, thereby hindering the venous return as little as possible.

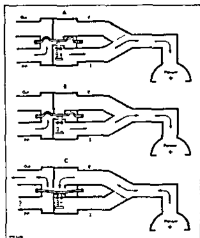
Fig. 11, 12 and 13 show a valve[51] which we have now used for about a year and which has made absorbers unnecessary. Another method is simply to run a high flow (see fig. 14) If the flow is 15-20 litres per minute the absorber is not necessary, but in that case adequate humidification is particularly important.

Right from the beginning of the 1952 epidemic we have worked on mechanizing the bag ventilation method Some such methods did already exist, and several types of apparatus have since been developed and used for long periods of time

FIG. 11. NON-RETURN RESPIRATION VALVE



FIG 12. FUNCTION OF RATTENBORG NON-RETURN RESPIRATORY VALVE



A = positive-pressure inspiration
B = spontaneous inspiration
C = expiration
PP = positive pressure E = expiration
I = inspiration

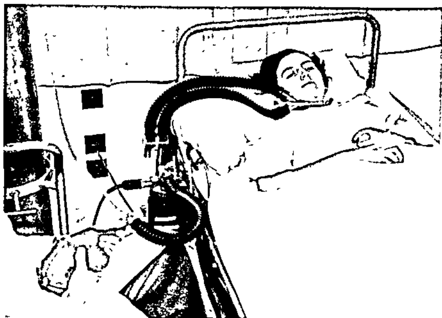
Engström respirator

This is a flow-sensitive respirator designed for intratracheal, intermittent positive-pressure breathing It can be used with a mask, but is more effective if the patient has a tracheotomy. It is rather complicated (see fig 15), and requires thorough understanding of its mechanical and ventilatory properties, but it is a very reliable and robust machine We have used it on quite a few acute, "wet" patients with relatively satisfactory results, and as a whole the Engström machine has in our hands proved more effective than ordinary tank respirators in the acute stage The inspiration phase is only half the length of the expiration phase, but this ratio can easily be changed In my opinion this respirator should have a thorough trial with acute patients. In the newest model expiration is assisted by suction

The price is about $3,000

Manufacturers · Mivab, Stockholm, Sweden

FIG. 13. MANUAL BAG VENTILATION WITH ELECTRIC HUMIDIFIER AND NON-RETURN RESPIRATION VALVE*



* See fig 12

Gullberg attachment

The intratracheal positive-pressure aggregate designed by Gullberg and attached to the Kifa cuirass respirator (see fig 7) has been constructed essentially on the same lines as the Bennet positive-pressure attachment.[8]

A small bellows is synchronized with the big bellows of the Kifa respirator, rhythmically blowing air into the patient via an endotracheal tube Pressures can easily be kept within physiological limits, and since the apparatus is cam-actuated it is possible to produce a "physiological" pressure curve There is no suction in the expiratory phase.

In the post-acute phase this machine proved very valuable in tracheotomized patients. It is extremely reliable and may be used with the Kifa cuirass. The extra cost of furnishing the Kifa respirator with the Gullberg attachment is not very high. It is a good respirator for the weaning period, because the attachment can quite easily be gradually discarded, thus making it possible to close the tracheotomy

Manufacturers: Kifa, Stockholm, Sweden

Price: $300-400.

Bang respirator [8]

This is a pressure-sensitive electrical respirator specifically designed for mechanizing manual bag ventilation (fig 16, 17, and 18) It is quite an ingenious solution of the problem, and has proved very effective in many patients in post-acute and chronic stages The respirator can be so set that " physiological " pressure curves are obtained (see fig 19), and in the newest type suction is applied to the expiratory phase A very effective humidifying aggregate is attached (see fig 20), securing 100% humidity at

FIG 14 POSITIVE-PRESSURE VENTILATION WITHOUT ABSORBER — " FINGER VENTILATION "



body temperature This is done by warming the efferent rubber tubes electrically We have used this machine only a few times in acutely ill, " wet " patients, but it seems to work quite satisfactorily, and the newest type, with suction during expiration, should be well worth trying in such patients with a cuff-tube, i e , ventilated in a closed system without much leakage When the cuff-tube is replaced by an ordinary silver canula, where leakage is

considerable, the Bang respirator is still effective when the patient is awake, but during sleep this pressure-sensitive respirator quite often stops because of too much leakage (open mouth).

The price of the Bang respirator is only one-fourth to one-eighth of that of a cuirass or tank respirator

Manufacturers. Bang and Olufsen, Struer, Denmark.

FIG. 15. THE ENGSTRÖM RESPIRATOR



Aga respirator

This is a pressure-sensitive respirator (see fig 21 and 22), based on the ejector system, the driving force is compressed air or a compressed oxygen mixture The Aga is thus independent of electric current It is easy to handle and extremely reliable, and has been used for more than a year in chronic patients with satisfactory results We have no experience with it in acute patients, but no doubt it could also be used in the acute phase.

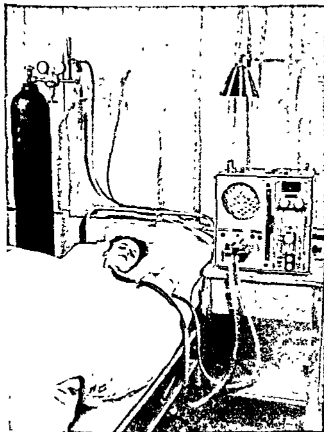
The maximal inspiratory capacity is 60 litres per minute. During expiration the pressure comes abruptly down to 2 mm of water with a flow of

25 litres per minute. As with the Bang respirator, the pressure-regulated Aga machine stops if there is too much leakage

The price is about $400

Manufacturers: Aga Gas Accumulator, Stockholm, Sweden

FIG 16. THE BANG RESPIRATOR



Rocking bed

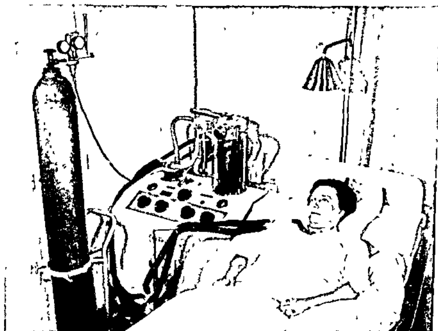
As the mechanical rocking bed should be used only in " dry " cases of respiratory poliomyelitis with a not too severe reduction of vital capacity,

considerable, the Bang respirator is still effective when the patient is awake, but during sleep this pressure-sensitive respirator quite often stops because of too much leakage (open mouth)

The price of the Bang respirator is only one-fourth to one-eighth of that of a cuirass or tank respirator.

Manufacturers Bang and Olufsen, Struer, Denmark.

FIG. 15 THE ENGSTRÖM RESPIRATOR



Aga respirator

This is a pressure-sensitive respirator (see fig 21 and 22), based on the ejector system ; the driving force is compressed air or a compressed oxygen mixture. The Aga is thus independent of electric current. It is easy to handle and extremely reliable, and has been used for more than a year in chronic patients with satisfactory results. We have no experience with it in acute patients, but no doubt it could also be used in the acute phase.

The maximal inspiratory capacity is 60 litres per minute. During expiration the pressure comes abruptly down to 2 mm of water with a flow of

FIG 18 THE BANG RESPIRATOR IN ACTION LATEST MODEL WITH ELECTRIC HUMIDIFIER

FIG 19 PRESSURE CURVE, BANG RESPIRATOR

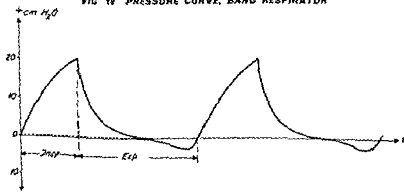
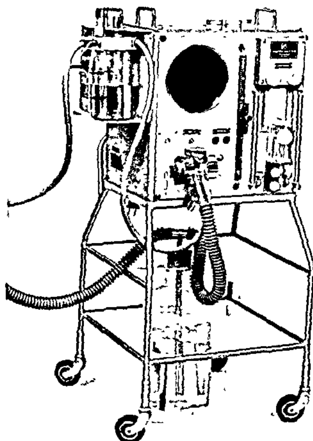


FIG. 17. THE BANG RESPIRATOR: LATEST MODEL WITH ELECTRIC HUMIDIFIER



its place in the treatment of acute poliomyelitis with respiratory failure is limited. On the other hand, it is often very useful in the weaning period and the chronic stage, and probably has a beneficial effect upon the circulation and muscle tone (see fig 23)

Electrophrenic respirator [83]

This has been used only a few times in our hospital, and without convincing results. It is a type of ventilation difficult to administer, requiring

OTHER TREATMENT IN ACUTE RESPIRATORY POLIOMYELITIS

Postural Drainage

The importance of placing in a postural-drainage position *patients who* show even the slightest tendency to accumulate secretions in the airway can hardly be exaggerated As the declivity of the trachea from the axis of the body is about 20° the patient should be tipped somewhat more than 20° in the supine position to make use of gravitational forces in clearing the airway.[23] Most adult persons do not tolerate such a position very well, since it tends to aggravate intracranial pressure. Effective postural drainage is much easier to produce if the patient is in the prone or semi-prone position, with the head to one side and the body placed in a jack-knife position with the pelvis high and the head and feet low (see fig. 2, page 187) In this way many patients with polioencephalitis or bulbar poliomyelitis without spinal respiratory insufficiency can be tided over, given that *secretions are* thin In dehydrated patients with viscid secretions, postural drainage and suction through the mouth or nose are often ineffective Unfortunately, *effective* postural drainage and mechanical respiration can only rarely be carried out simultaneously

Suction

Intermittent or continuous suction is very important in maintaining an unobstructed airway In my opinion it should not be continuous, but intermittent according to the needs *of the patient* Relying on [illegible]

[illegible]

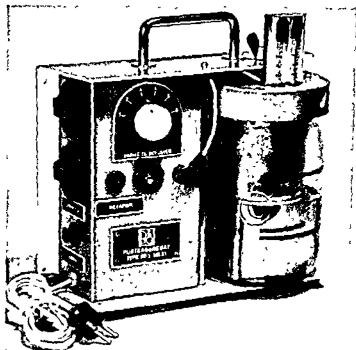
branes are not tr[illegible]
thick, it is often [illegible]

Stomach-Tube

In all cases with the slightest impairment of swallowing, or ileus with gastric atonia, an in-dwelling stomach-tube should be inserted under constant suctioning in order to keep the stomach empty. When all danger of gastric regurgitation has passed, the tube can be used for feeding *purposes*

a physician continuously at the bed-side, and it cannot be used for prolonged periods of time

FIG. 20. CLOSE-UP OF ELECTRIC HUMIDIFIER, BANG RESPIRATOR



The advantages of the method are [66]

(1) it tends to augment venous return, because inspiration is obtained with negative rather than positive intrapleural pressure;

(2) this type of mechanical respiration is flexibly adjustable in regard to all the essential components of the respiratory cycle;

(3) the reserve of the method is great,

(4) in cases of poliomyelitis with respiratory-centre involvement and erratic, irregular respiration, the electrophrenic respirator inhibits such irregularities, thus permitting effective pulmonary ventilation.

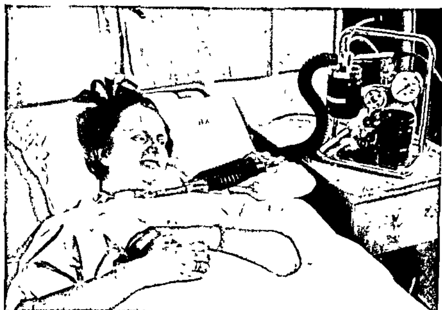
FIG. 22. AGA POSITIVE-PRESSURE RESPIRATOR WITH NON-RETURN VALVE: II



The task of the nurse is one of constant vigilance, observing incipient symptoms of complications, attending to them if within her competence, and calling medical aid in time if necessary The position of the patient should be changed frequently in order to prevent congestion and atelectasis in dependent portions of the lung The skin should be attended to carefully in order to prevent friction and bed-sores, and in addition, patients with severe peripheral paralysis have a multitude of little personal needs that should be understood and relieved

Finally, it is of the utmost importance to prevent exhaustion—to take care lest too much attention and too much treatment precipitate dangerous

FIG 21. AGA POSITIVE-PRESSURE RESPIRATOR WITH NON-RETURN VALVE. I



Other Treatment-Methods

Treatment purporting to prevent complications or to counteract complications when present has already been touched upon It consists in maintaining normal fluid, electrolyte, and protein balance, counteracting vasomotor shock and cardiac and renal failure, and combating secondary bacterial infection

Expert lung physiotherapy (squeezing, tapotement, cough-exercise) is extremely important in order to prevent lung complications.

Plasma- or blood-transfusions should be used when needed.

The indications for applying hot fomentations to the chest are just as reasonable or unreasonable as the indications for using them on the extremities. We used them very extensively Whatever their somatic value may be, their symptomatic and psychological effect is considerable.

Nursing Care

Every patient with acute bulbar or respiratory poliomyelitis should constantly have a personal, trained nurse at his bed-side

WEANING PROBLEMS IN PROLONGED ARTIFICIAL RESPIRATION

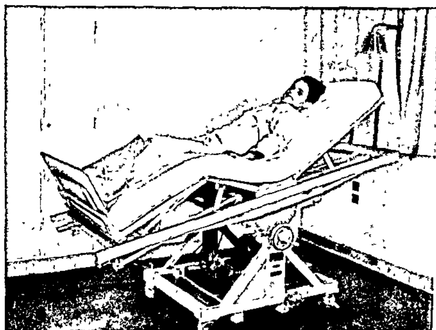
The object of treating a patient with respiratory insufficiency, whether central in origin or spinal—or both—is to tide him over the acute, life-threatening phase of the disease in the hope that an adequate number of ganglion cells in the medullary centre and spinal motor units representing the respiratory muscles will eventually recover sufficiently to produce enough spontaneous ventilation to secure independence of mechanical aid. For the patient, the difference between a life more or less dependent upon mechanical ventilation and a life—even a restricted one—independent of respirators is inestimable

Judging from the general impression of a comparatively favourable prognosis of paralysis of the cranial nerves—the lower as well as the upper group, where severe, residual paralysis is rather rare—it might be thought that the medullary centres had a similar chance of recovery Yet, studying microscopic sections of the reticular formation in autopsy material from acute patients, it is hard to believe that the changes found would ever be compatible with adequate function of the respiratory centre In these cases we often find very extensive damage, with disappearance of the majority of ganglion cells. Such changes must be irreparable, and as we never see patients surviving with symptoms attributed to subnormal function of the medullary centres of respiration[7]—i e , patients with sufficient power of the respiratory muscles to maintain adequate ventilation, but with the irregular type of breathing characteristic of damage of the medullary centres —we are forced to assume that all patients who regain sufficient muscular power to keep up adequate ventilation have a normally functioning respiratory centre Chronic respiratory failure is purely spinal.

On the other hand the different respiratory muscles seem to share in the general prognosis of the skeletal muscles, with the possible exception of the diaphragm For the others it is usually the rule that the higher the degree of paralysis after the acute stage, and the longer it takes before recovery starts, the less favourable is the prognosis and the less can it be expected that adequate functional power will ever return On the other hand, the two halves of the diaphragm, innervated from the third to the fifth cervical segments, seem not always to follow this pattern, as late recovery, even after four to six months of complete paralysis, does occur From the point of view of ventilation, it is important to stress that unilateral diaphragmatic paralysis is very common in poliomyelitis with respiratory insufficiency

fatigue. It is difficult in the acute stage to secure good rest and substantial periods of sleep, but this very important point should not be neglected; some most experienced clinicians maintain that fatigue in itself may be fatal.[52, 68]

FIG. 23. EMERSON ROCKING BED



Psychological Aspects

Psychological support is important even in the acute stage of bulbar and respiratory poliomyelitis, but naturally becomes even more important [illegible]

If the patient shows signs of returning spontaneous breathing, the next step is either to stop the motor or to open the side ports, and observe the patient's respiratory efforts in the machine This should be repeated rather often but not kept up to the point of exhaustion, and should certainly be broken off before the appearance of cyanosis and before symptoms of carbon dioxide retention arise In the beginning it is advisable to measure the blood pressure at short intervals, and to put the patient back on artificial respiration if the blood pressure goes up

In the majority of cases with respiratory insufficiency recovery begins early The earlier recovery sets in, the better is the ultimate prognosis Very often after the first stormy days, when the virus infection has burnt itself out and vascular complications and secondary bacterial infection are under control, recovery proceeds quickly, measurable by increasing vital capacity and by the steadily increasing periods of time during which the patient can be out of the respirator without discomfort

The biochemically conditioned weaning difficulties have been mentioned, and also the adverse psychological factors presumably based mainly on fear These psychological factors can best be dealt with by gently exposing their groundlessness, demonstrating to the patient that there is no reason for fear, and that falling asleep will not kill him When spontaneous respiration comes back it is often irregular and thus cannot be assisted mechanically Here manual bag ventilation is of value because it can be individualized as much as is required

Apart from the psychological factors, certain other complications may lengthen the weaning period , first, persistent infection in the upper airway, gradually becoming resistant to all known antibiotics Such intractable infection of the bronchial tree was quite common in our patients, and after some time established itself as nosocomial Yet it only rarely seemed to be the sole causative factor of death, and eventually always cleared up when spontaneous respiration returned and the tracheotomy wound could be closed

Respiratory cripples, those in respirators as well as those leading a precarious life with a greatly reduced vital capacity, very easily become victims of non-specific, contagious infections of the upper airway, resulting in bronchitis, bronchopneumonia, and atelectasis, giving rise to a serious, although temporary, setback All personnel with even the slightest cold or sore throat should therefore keep away from the wards, and treatment with specific antibiotics should be prompt

Most of our respiratory invalids were immunized against influenza, and children should be vaccinated against whooping-cough and tuberculosis If exposed to measles, they should have gamma globulin

Naturally, respirator treatment should be of the shortest possible duration, although the patient should not be urged to breathe without mechanical aid at all costs, because then a set-back is likely to occur. As usual it is " la juste nuance " that counts, based on intelligent appreciation of the patient's somatic and psychological reserves of strength. Here, of course, as the latter cannot be measured, the temperament and insight of the doctor in charge come into the picture It is a good thing for a doctor to be enthusiastic, but it is even better to make the patient enthusiastic, concentrating all his energy on regaining independence of mechanical aid A great deal can be achieved by patiently teaching such cases how best to use the available muscle power—for instance by frog breathing—but there is no doubt that in the weaning period inhibiting psychological factors originating from an understandable fear neurosis are of considerable importance.

Some few patients with respiratory insufficiency become chronic respirator cases because of an unconquerable neurosis based on fear. Most often the patient fears that he will suffocate if he loses consciousness, i e , if he falls asleep This, evidently, is the reason why some chronic respirator patients can be up and about in the daytime, but insist on sleeping in the respirator at night In the great majority of cases, however, muscular power gives out after shorter or longer periods of time because of fatigue, respiration becoming too laboured If, in such patients, repeated arterial blood-samples are taken during their time outside the respirator, a gradual increase of carbon dioxide tension with eventual lowering of pH (respiratory acidosis) can be observed, usually long before there is any appreciable decrease of oxygen saturation In such cases the need for mechanical aid can thus be objectively demonstrated This is not the case in the neurotic type of patient

Weaning should start as early as is practicable, first of all by cutting down as far as possible without too much inconvenience the help given by the respirator In practice it is a fact that if the airway is free artificial respiration always tends towards hyperventilation This—if moderate—is not directly harmful, but should be avoided at all costs, because prolonged hyperventilation with low carbon-dioxide tension is conducive to lowered sensitivity of the respiratory centre The patient gets used to low carbon dioxide tension, which makes it more difficult for him to accustom himself to spontaneous breathing, often a vicious circle is set up, resulting in a respirator-fast patient with chronic hyperventilation; this should be avoided

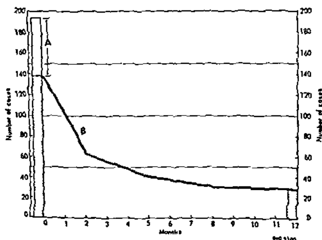
This is best counteracted by reducing the rate of the machine to 10-14, and especially by decreasing pressures, resulting in smaller volumes of tidal air. In this way it can be estimated whether the patient is capable of adding to the respiratory aid offered by the machine through his own muscular force when the ventilatory performance of the respirator at a given setting is known

TABLE VII. DEATHS IN 333 PATIENTS WITH RESPIRATORY INSUFFICIENCY: OBSERVATION PERIOD 12-18 MONTHS

Group	Number of patients	Deaths		Time of death					
		number	percentage	before 24 hours	24 hours to 3 days	3 days to 7 days	7 days to 14 days	14 days to 1 month	after 1 month
A	75	29	39	13	8	5	2	1	0
C	157	48	30	9	18	11	7	2	1
D	28	13	46	2	7	1	1	0	2
E	60	38	63	1	8	10	11	3	5
F	13	11	85	1	3	0	1	5	1
Total		139	42	26	44	27	22	11	9
Percentage of 139				19	32	19	16	8	6

Of the 194 patients surviving with respiratory insufficiency (333 − 139 deaths) 56—or one-sixth of the total—did not require artificial respiration More than half those who did (57%) were back to permanent spontaneous respiration in less than two months. Up to this point the curve is straight

FIG 24. TOTAL DURATION OF ARTIFICIAL RESPIRATION IN 194 SURVIVING PATIENTS WITH RESPIRATORY INSUFFICIENCY



Date of reference 1 January 1954
A = 56 patients with respiratory failure not requiring artificial respiration
B = 138 patients requiring artificial respiration

In some few cases—five—with a tracheotomy, tracheal stenosis developed after several months. This, of course, also made total independence of mechanical aid difficult

Two years after the 1952 epidemic, apart from about 20 patients continuously requiring mechanical respiratory aid, we still have a few with such low vital capacities and easily exhaustible muscular power, frozen chests, lungs with reduced compliance,[19] and fibrous, nearly immobile diaphragms, that they still are, and probably always will be, partly dependent on mechanical respiration Very few of these unfortunates ever ask the dreaded question " Doctor, shall I ever get out of this machine ? " In my opinion it is hardly ever justifiable—if not asked—to tell a patient that he will never become independent of the respirator Most of our respiratory cripples are quite young and presumably may live for many years—maybe 20 years or more Even in the relatively few cases where I have encountered this question I have always felt it my duty to evade a straightforward answer—invariably to the obvious satisfaction of the patient, who does not press the question Days spent in relative comfort and optimism are never regretted, and no patient has ever blamed me for trying to temporize I do not consider it my task strictly to follow personal laws of formal ethics at the expense of my patient As doctors, we must always keep in mind that if we cannot effect a cure it is our duty to do our best to console. In this respect women are often much more gifted than men ; our nurses and physiotherapists have done wonders to keep our patients in good spirits

EVOLUTION AND REGRESSION OF RESPIRATORY INSUFFICIENCY

In the Copenhagen epidemic of 1952, 345 patients admitted to the hospital required special therapeutic measures because of respiratory insufficiency, impairment of deglutition, or both As 12 of these (group B, table I (see page 164)) did not have respiratory failure, 333 remained with some degree of deficient ventilation Of these 139 (42%) have died up to 1 January 1954

Table VII shows that in half the patients who died sooner or later with symptoms of respiratory insufficiency, with or without deficient swallowing, death occurred within the first three days in hospital, in 70% within seven days, in 86% within 14 days, by one month after commencement of respiratory failure 94% of all deaths had taken place (observation period : 12-18 months).

Fig. 24 shows the duration of artificial respiration in 194 surviving patients with respiratory insufficiency (T. Sottrup, personal communication).

found among the 105 patients with paralysis of both the thoracic respiratory muscles and the diaphragm

Diaphragmatic paralysis, diagnosed fluoroscopically, was very common in our respiratory patients The total was 133 cases with or without intercostal involvement, 60 unilateral (39 right side, 21 left side), and 73 with bilateral diaphragmatic weakness or paralysis.

As mentioned before, diaphragmatic recuperation may start very late, but most often, if paralysis is not too severe, recovery begins early A detailed study of our many cases of weakness or paralysis of the diaphragm is now in progress, and will be published at a later date. So far, very little is known about the prognosis of diaphragmatic paralysis.

In conclusion, it may be said that the prognostically unfavourable features are:

(1) continuous artificial respiration all round the clock for more than one month,

(2) severe bilateral upper paraplegia or quadriplegia,

(3) simultaneous intercostal and diaphragmatic paralysis

THE CHRONIC RESPIRATOR PATIENT

In our experience only one in ten patients requiring continuous artificial respiration one month after the acute stage ever becomes independent of mechanical respiratory aid The same is true of patients who, three months after the commencement of mechanical respiration, are still in need of it for a considerable part of the day Yet it should be kept in mind that the diaphragm may start very slowly to regain contractility I remember one boy who had respiratory insufficiency of pure spinal origin and was put in a cuirass respirator After six weeks his costal muscles had regained sufficient strength for him to be taken to the x-ray department Fluoroscopy showed that the right side of his diaphragm moved maximally 1 cm, while the left was immobile Four weeks later he could leave the respirator The condition of his diaphragm at that time was the same—0 cm and 1 cm—until five months after onset. It was then that his diaphragm first started to come back, we followed the recuperation closely, doing fluoroscopy every two weeks, and 12 months after the acute stage, function was normal. This was naturally of great moral help in the 1952 epidemic, because it proved that even late recoveries may occur It gave us hope Unfortunately, thousands of fluoroscopies since that time show that late recovery of the diaphragm is exceptional

and steep. During the next three months the recovery-rate slows down. Yet one-third of those requiring artificial respiration after two months become totally independent in the course of the next three months. Thus, after five months 60% of those alive one month after starting artificial respiration have recovered (it should be borne in mind that nearly all deaths (94%) take place within this first month). During the next three months—from the fifth to the eighth—a further slowing-down is observed; nevertheless, one-fourth (10 out of 42) become independent of respiratory means. Between 12 and 18 months, two of the remaining 29 recovered; from this point the recovery curve is nearly asymptomatic and after one year of artificial respiration the patient must be regarded as a chronic respirator patient.

One month after the commencement of artificial respiration 102 patients were in need of mechanical aid, 43 of them continuously. These 43 patients include the 27 cases who must now be considered incurable.

That respiratory paralysis was very severe in the 1952 epidemic in Copenhagen is illustrated by the fact that, of a total of 333 patients with deficient respiration, 139 died and 43 (55%) required continuous artificial respiration all round the clock one month after onset.

The evolution time of respiratory insufficiency and its relation to death-rates is shown in table VIII.

TABLE VIII EVOLUTION OF RESPIRATORY INSUFFICIENCY IN RELATION TO DEATH-RATES

Evolution time of respiratory paralysis	Number of patients	Number of deaths	Case mortality (%)
Less than 2 days	160	84	53
More than 2 days	149	49	33
Not known	24	6	(25)
Total	333	139	42

It can be seen that half the cases develop during the first two days after onset of the meningitic phase of the disease. Only very few cases of respiratory failure are diagnosed later than from seven to ten days after the start of meningitic symptoms, however, and they very rarely become chronic.

In our series all patients with paralysis of either the intercostals or the diaphragm eventually recovered, and the 27 chronic patients are all to be

found among the 105 patients with paralysis of both the thoracic respiratory muscles and the diaphragm.

Diaphragmatic paralysis, diagnosed fluoroscopically, was very common in our respiratory patients. The total was 133 cases with or without intercostal involvement, 60 unilateral (39 right side, 21 left side), and 73 with bilateral diaphragmatic weakness or paralysis.

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The chronic respirator patient always has total or subtotal peripheral paralysis. He is in the most pitiful state any patient can possibly be, and requires our unremitting psychological and medical support. Treating the chronic respirator patient demands ingenuity and understanding. His fighting spirit is usually remarkable, but periodic mental depressions are inevitable and should be met halfway with comprehension and affection. This is certainly not easily achieved, and is even harder to maintain year in and year out, but it should always be attempted by the nurses and internes, and especially by the physician in charge.

Which type of respirator is best for a chronic patient cannot be determined with certainty. It is a well-established fact that body and cuirass respirators can be used for many years, and our experience has shown that intratracheal positive-pressure respiration can be kept up for at least two years. Each type of respirator undoubtedly has its advantages and disadvantages in the chronic stage. I have asked some of our permanent respirator patients if they would prefer being in a tank respirator with their tracheotomy closed. They all said no, " because then we could never sit up, never get out of bed, and could not be kept clean ". That they cannot speak very well with a tracheotomy does not seem to bother them much; they can talk during expiration and while without mechanical respiratory aid.

Nursing care is also extremely important in the chronic stage, and, more than ever, good care of the skin is essential. The food problem is also important, as it generally takes many months before a respirator patient regains his appetite and often more than half a year before he starts putting on weight. In these immobile patients enormous demineralization is encountered, which cannot be counteracted by dietary means. The urine should be kept acid and infection combated in order to inhibit formation of renal stones. We have seen a few cases of " spontaneous " bone fractures.

As the great majority of chronic patients have little or no muscular power in their fingers and arms, they are practically helpless and totally dependent on the nursing staff. This absolute dependence should always be kept in mind, together with the fact that for a time it may make the patient antagonistic or even aggressive. To me it is a marvel that any chronic respirator patient can go on being an " easy " patient month after month, but they usually are. If muscle power permits, everything possible should be done to reduce their pitiful helplessness. Children should have school-teachers, and adults educational lessons and books according to their taste, and their intellectual and cultural standpoint. This is important in order to keep up morale, as are good music, films, and television.

The patients' relatives can do much to mitigate their lamentable condition and should be encouraged to shoulder the burden of taking them home—even in a respirator—whenever economically and psychologically possible.

TABLE IX THERAPEUTIC RESULTS IN LIFE-THREATENING POLIOMYELITIS

Clinic	Period	Classification	Cases	Deaths (%)
Blegdam Hospital Copenhagen, Denmark [illegible]	1934–44	Respiratory paralysis without bulbar involvement	17	28
		Respiratory paralysis with bulbar involvement	51	94
		Respiratory paralysis of undetermined types	8	100
Oslo, Norway [illegible]	1936–45	*Respiratory paralysis without* bulbar involvement	34	68
		Respiratory paralysis with bulbar involvement	27	93
Sweden [illegible]	1934–45	Respirator cases	834	86
Minnesota, USA [illegible]	1948	Respiratory centre group	36	69 } 61
		Circulatory centre group	12	83 } 61
		Encephalitic group	15	7 } 61
		Combined bulbo-spinal group	20	75 } 61
Wisconsin, USA [illegible]	1940–51	Bulbo-encephalitic	33	21
		Bulbo-autonomic centres	62	95
		Bulbo-cranial nerves	153	16
		Bulbo-spinal	163	25
England [illegible]	1947	Respirator patients	560	57
Evanstone Hospital, USA [illegible]	1947–8	Bulbar and bulbo-spinal	15	0
Chicago Residents, USA	1948	Bulbar and bulbo-spinal	49	39
Illinois, outside Chicago, USA	1947–8	Bulbar and bulbo-spinal	105	39
Evanstone Hospital, USA	1947–52	Bulbar and bulbo-spinal	129	19
Illinois, outside Chicago, USA	1947–51	Bulbar and bulbo-spinal	722	38
Los Angeles, California, USA [+]	1946	Respirator patients	45	79
	1947	Respirator patients	21	67
	1948	Respirator patients	294	42
	1949	Respirator patients	130	17
Blegdam Hospital, Denmark [illegible]	1952	Encephalo-bulbar	87 } 345	37 } 41
		Spinal respiratory paralysis	157 } 345	30 } 41
		Bulbo-spinal	101 } 345	61 } 41

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The patients' relatives can do much to mitigate their lamentable condition and should be encouraged to shoulder the burden of taking them home—even in a respirator—whenever economically and psychologically possible.

TABLE IX. THERAPEUTIC RESULTS IN LIFE-THREATENING POLIOMYELITIS

Clinic	Period	Classification	Cases		Deaths (%)	
Blegdam Hospital Copenhagen, Denmark [44]	1934–44	Respiratory paralysis without bulbar involvement	17		28	
		Respiratory paralysis with bulbar involvement	51		94	
		Respiratory paralysis of undetermined types	8		100	
Oslo, Norway [36, 39]	1936–45	Respiratory paralysis without bulbar involvement	34		68	
		Respiratory paralysis with bulbar involvement	27		93	
Sweden [9]	1934–45	Respirator cases	834		86	
Minnesota, USA [42]	1946	Respiratory centre group	36		69	61
		Circulatory centre group	12		83	
		Encephalitic group	15		7	
		Combined bulbo-spinal group	20		75	
Wisconsin, USA [22]	1940–51	Bulbo-encephalitic	33		21	
		Bulbo-autonomic centres	62		95	
		Bulbo-cranial nerves	153		16	
		Bulbo-spinal	163		25	
England [9]	1947	Respirator patients	560		57	
Evanstone Hospital, USA [33]	1947–8	Bulbar and bulbo-spinal	15		0	
Chicago Residents, USA	1948		49		39	
Illinois, outside Chicago, USA	1947–8		105		39	
Evanstone Hospital, USA	1947–52		129		19	
Illinois, outside Chicago, USA	1947–51		722		38	
Los Angeles, California, USA [9]	1946	Respirator patients	48		79	
	1947		21		67	
	1948		294		42	
	1949		130		17	
Blegdam Hospital, Denmark [34, 44]	1952	Encephalo-bulbar	87	345	37	41
		Spinal respiratory paralysis	157		30	
		Bulbo-spinal	101		61	

RESULTS OF TREATMENT OF BULBAR AND RESPIRATORY POLIOMYELITIS

Unfortunately it is impossible to compare the therapeutic results from different clinics, because spontaneous variations of the prognosis of poliomyelitis are very great and because clinical classification and indications for different types of treatment vary so much, and usually are not stated. Many authors mention only one group, the respirator patients, but if their criteria for putting a patient into a respirator are not known we are at a loss to interpret the therapeutic results. Even in the excellent paper reporting the results in Los Angeles from 1946 to 1949 [8] there is no classification of the life-threatening cases, and no criteria are stated for the different measures used. Naturally, death-rates should refer only to life-threatening cases and not to all paralytic cases, let alone to all cases of poliomyelitis. Nevertheless, in table IX I have computed results of treatment of life-threatening poliomyelitis from the scanty literature. The list is no doubt incomplete [6, 8, 9, 22, 23, 26, 30, 33, 34, 46]

From the data presented here it is very difficult to draw definite conclusions. Yet it seems as if the extremely grave prognosis of ten years ago has improved somewhat, probably because of a growing realization that the most important problem in life-threatening poliomyelitis is respiratory—the maintenance of an open airway.

TABLE X MORTALITY-RATES IN 331 CONSECUTIVE PATIENTS WITH LIFE-THREATENING POLIOMYELITIS

Group	Hospitalization time	Number of cases	Deaths	
			number	*percentage*
I	7/7 – 25/8	31	27	87
II	26/8 – 8/9	50	27	54
III	8/9 – 23/9	50	25	50
IV	23/9 – 5/10	50	20	40
V	6/10 – 21/10	50	13	26
VI	21/10 – 6/11	50	18	36
VII	6/11 – 23/12	50	11	22
Total II – VII		300	114	38

Note: Bag ventilation was introduced on 26 August

In the Copenhagen epidemic of 1952 results steadily improved throughout the epidemic period, despite the unabating severity of the fresh cases Before 26 August, when the first case was treated with manual positive-pressure ventilation, we received 31 patients requiring special therapeutic measures, of whom 27 died. From that date until Christmas, 300 patients were treated along the new lines with the results shown in table X.

Table X shows that the mortality-rate for these 300 consecutive patients, of whom the great majority were treated by tracheotomy and bag ventilation, was gradually reduced from over 80% to about 40%, representing about 120 lives [33]

Without doubt in recent years some progress has been made in the treatment of bulbar and respiratory poliomyelitis, but we still have much to learn.

As the optimal therapy of the life-threatening cases of poliomyelitis requires much special knowledge and extensive experience, this treatment should be concentrated in rather few specifically equipped and well-staffed centres At the same time, insight in preliminary treatment should be common knowledge to all hospitals treating poliomyelitis, in order to obtain the best possible results.

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V	6/10 – 21/10	50	13	26
VI	21/10 – 6/11	50	18	36
VII	6/11 – 23/12	50	11	22
Total II – VII		300	114	38

Note. Bag ventilation was introduced on 26 August

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VIROLOGY

THE VIRUS OF POLIOMYELITIS

Physical and Chemical Aspects

SVEN GARD, M.D.

Professor of Virus Research, School of Medicine, Karolinska Institutet, Stockholm, Sweden

Definition

The problem of the classification of viruses in general is in a state of great confusion and it has so far been impossible to reach an agreement as to the principles to be applied Two separate international committees are studying the question one—a subcommittee of the Nomenclature Commission of the International Botanical Congresses—is concerned exclusively with plant viruses, the other—the Virus Subcommittee of the Permanent International Committee on Bacteriological Nomenclature of the International Association of Microbiologists—is concerned with all viruses For the time being, therefore, no strict definition of the virus of poliomyelitis can be presented

There is, of course, a definition inherent already in the current term "poliomyelitis virus"—which is to say, an infectious agent classifiable as a virus and capable of producing in man the clinical and pathological picture of typical poliomyelitis This might seem straightforward enough and yet the very fact that the definition is based upon clinical and histopathological criteria has threatened to obscure the issue It is now generally agreed that cases answering the description of the typical disease represent only a minor fraction of all those who contract the infection. The milder forms of the disease are clinically indistinguishable from certain manifestations of infection by such agents as, for example, the viruses belonging to the Coxsackie group. From a purely clinical point of view it might seem logical to group together viruses capable of causing identical or similar syndromes Attempts at classification on such a basis have in fact been made (Mollaret,[40] Jungeblut [29])

From a microbiological point of view such systems of classification are irrational The symptoms produced are only partially determined by the properties of the infectious agent, by and large, host factors are more important The microbiologist, therefore, is inclined to view the problem

human origin. The first strain of this virus ever to be isolated was encountered by Jungeblut [19] in attempts to adapt to cotton rats and mice the so-called Y-SK strain of type 2 poliomyelitis virus Although Jungeblut's results have never been satisfactorily explained, the isolation of his virus (Col-SK) is in most quarters considered as a laboratory pick-up It appears to have been proved that the virus is immunologically distinct from the alleged parent strain, and as it also deviates with regard to certain chemical properties, the assumption of a transition of one virus into the other seems extremely unlikely

The Coxsackie viruses present their own problems Like the virus of poliomyelitis, they are found in or on the mucous membranes of the digestive tract of infected persons and are excreted with the pharyngeal secretions and the stools Their dissemination, therefore, is favoured by the same external factors as that of the poliomyelitis virus and they tend to appear with the latter virus in mixed epidemics Epidemiologically as well as clinically (see earlier paragraphs) the Coxsackie and poliomyelitis viruses form parts of the same pattern, which explains why attempts have been made to group them together They may also be related in a microbiological sense but available data indicate a relationship, if any, on a different level from that which holds for the viruses of poliomyelitis and mouse encephalomyelitis In addition, the Coxsackie group is apparently not homogeneous, it is very probable that some of its present members will be classified differently in the future At the present moment, therefore, inclusion of the Coxsackie viruses in the poliomyelitis group would be unwise and misleading, a premature fusion of the groups might easily develop into confusion

To summarize, the use of the term "poliomyelitis virus", or combinations thereof, should be confined to the designation of strains of virus which conform immunologically to one of the type strains—Brunhilde, Lansing, and Leon—or to Theiler's GD I In this article these strains will be designated respectively *Poliovirus hominis*, type 1, 2, and 3, and *Poliovirus muris*

Purification

In the study of viruses tools have been used and methods devised that differ essentially from those applied in other fields of microbiology In some respects the virological technique resembles enzyme chemistry rather than bacteriology For different reasons many properties of viruses can be assessed only if the agents under study are available in a pure state In this connexion the word "pure" has to be taken in its chemical sense, meaning absence of chemical impurities, but not in the bacteriological

from a different angle from the clinician; to look upon an infectious disease exclusively as an etiological entity, and to disregard all variations in symptomatology His ultimate goal is an unequivocal identification of the virus entirely by its own properties, with complete disregard of the way in which an incidental host organism might react to infection by it. As this goal cannot yet be attained, a compromise is necessary Three agents capable of producing typical poliomyelitis in man and sufficiently similar microbiologically to be regarded as types of one virus are now known Only a few of the physical and chemical properties of these agents are sufficiently well known or characteristic to aid in their identification; at present, therefore, heavy reliance must be placed in diagnosis upon immunological criteria

The virus of poliomyelitis may tentatively be defined as an infectious agent possessing certain physical and chemical properties (which are discussed later) and conforming immunologically to one of the three accepted type strains "Brunhilde" (type 1), "Lansing" (type 2), and "Leon" (type 3) This definition excludes, at least temporarily, such new immunological types of the virus as may be found in the future If this is in certain respects disadvantageous, a strict observation of the above criteria is also a safeguard against the indiscriminate adoption as poliomyelitis viruses of insufficiently studied new types The immunological properties are usually specific enough to prevent erroneous classification.

Although at present no rational comprehensive system of virus classification is possible, it is generally recognized that certain viruses fall into natural groups The poliomyelitis viruses, together with Theiler's mouse encephalomyelitis virus, seem to form one such group At the Sixth International Congress for Microbiology, held in 1953, the above-mentioned Virus Subcommittee recommended as a provisional name for this group *the generic equivalent Poliovirus with the species equivalents hominis for* poliomyelitis virus and *muris* for Theiler's virus [a] This terminology has been adopted in the present article

Other viruses considered in connexion with this group are the Teschen virus of swine encephalomyelitis, the Coxsackie group, and the encephalomyocarditis group of viruses Of these the Teschen virus is apparently more closely related to the poliomyelitis group than the others, although it has not been studied sufficiently thoroughly to make its definitive inclusion in the group appear justified

Certain strains of encephalomyocarditis virus were for some time regarded in many quarters as variants of that of poliomyelitis and have often been referred to in the literature as a murine poliomyelitis virus of

[a] The report of the Virus Subcommittee, presented by Dr C H Andrewes, is to be published in the *International Bulletin of Bacteriological Nomenclature and Taxonomy*

observations made on one of the members of the group are generally applicable to the others, data concerning *P muris* will be included if they add to available information about the human virus.

A partial purification of a tissue extract containing virus can be achieved in several ways. Impurities can be removed simply by centrifugation at moderate speeds which do not reduce the virus—for example, at 18,000 revolutions per minute (r p m) for 30 minutes, after treatment with ether some ether-soluble lipids can be removed with the organic solvent, and lipoproteins, insoluble in ether, can be transferred into a more hydrophobic condition, thus making them insoluble in water also and separable by centrifugation ;[13 18] several adsorbents, such as bentonite,[42] and certain ion-exchange resins[32] can be used for the removal of impurities, impurities can be precipitated with protamine sulfate,[63] cationic or anionic detergents (unpublished observations of the Department of Virus Research, Karolinska Institutet), or with streptomycin, storage at deep-freeze temperatures causes denaturation of certain nitrogen-containing substances without affecting the solubility of the virus[36]

Alternatively, the virus can be removed from a solution by high-speed centrifugation—for example, at 27,000 r p.m for 90 minutes,[13] by salting out (1/3 saturation with ammonium sulfate);[6] by precipitation with methanol at −5°C,[44] by adsorption onto alumina gel[51] or certain ion-exchange resins;[33] by adjustment of pH at 4 0-4 5[2 30]

By combining two or more of these procedures a considerable purification can be achieved Preparations of *P muris* strain FA, behaving in the ultracentrifuge as homogeneous macromolecular substances, were reported by Gard[13] and by Leyon[30] The very high specific activity of the preparations—2 to 10 × 10^{13} and approximately 10^{12} infectious units per gram, respectively—affords strong evidence in favour of the assumption that the preparations consisted of virus in an almost pure state The variations in specific activity observed may be accounted for by partial inactivation of the virus during the purification process

With regard to *P hominis*, interpretation of the results of published purification experiments is more difficult, as reliable homogeneity tests have usually not been carried out Loring & Schwerdt[36] reported the isolation from Lansing-infected cotton-rat brain of a homogeneous macromolecular fraction considered by them to represent the pure virus Their preparation had a specific activity of only about 10^9 infectious units per gram and a low sedimentation-constant not compatible with results obtained by other authors. It appears probable, therefore, that the preparation consisted mainly of a macromolecular substance present also in normal brains (Gard[13]), the virus representing less than 0 1% of the material The purpose of most of the other more recent studies was the preparation

sense, which implies merely the absence of other micro-organisms. The *purification of viruses is, therefore, of sufficient importance to deserve its* own chapter in the textbooks

Purification of poliomyelitis viruses has been considered to be a very difficult technical problem, and for very good reasons In each step of a purification process the virus has to be located in one of several fractions. No simple chemical reaction can serve this purpose because of the relative insensitivity of chemical methods, which prohibit the demonstration of the minute amounts of virus present Light or electron microscopy are equally useless Only by biological methods can the virus-content be assayed As long as the monkey was the only test animal available, a purification experiment on even a very modest scale presented considerable financial difficulties, insurmountable to most laboratories. The adaptation to mice of the Lansing strain improved the situation but accentuated other problems *One of the great difficulties stems from the comparatively* low virus-content of the starting material, which consists of nervous tissue from infected monkeys or mice Even well-adapted strains seldom yield more than 10^6 infectious units of virus per gram of tissue Gravimetrically this corresponds to something like 0 01-0 1 mg of virus per kg of tissue, or one millionth to ten millionths of 1% of the wet tissue The student of animal viruses has therefore reason to regard with envy the plant virologist who, in experiments with tobacco plants infected with mosaic virus, can find that as much as 80% of the total soluble protein is virus. To this should be added the fact that nervous tissue, because it is rich in lipoid matter, presents particularly difficult problems from a purification point of view

The introduction of the tissue-culture technique has radically changed the situation Production of large quantities of a comparatively pure starting material possessing a high initial virus concentration is now feasible and the problem of assaying the virus-content of different fractions has been reduced to insignificant dimensions However, in the last fifteen years a large number of different problems of immediate practical importance have accumulated, in expectation of the day when they might be successfully attacked That day has now dawned and laboratories all over the world are urgently occupied in looking for answers to all the questions asked In the initial stages of this investigation, the apparently less important problems have to await their turn, and so far no one seems to have found much time to spend on purely theoretical research As a result, practically all the data considered in this article date back to the pre-tissue-culture era Some of them are conflicting or unverified, and the whole subject is open to revision. More work has been carried out on *P. muris* than on *P hominis* Judging from present experience, the mouse virus has proved an excellent model virus, and as the results of

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TABLE I. DATA ON ULTRAFILTRATION THROUGH GRADOCOL MEMBRANES

Virus	Strain	Origin	APD* of membrane (μ)		Reference No
			passing virus	retaining virus	
P hominis	MV (Type 2)	monkey cord	35	30	57
	MV	monkey cord	40	27	8
	MV	monkey cord	58	13	29
	Lansing	mouse brain	230	110	28
	Lansing	mouse cord	50	41	38
	Lansing	mouse brain	200	50	38
	WS-48	human stool	300	50	38
P. muris	FA	mouse brain	35	27	58
	GD VII	mouse brain	35	27	58
	GD VII	mouse brain	32	8	38

* APD = average pore-diameter

filtration end-point being about 30 mμ Monkey-adapted strains of *P. hominis* types 1 and 3 and low-virulent strains of *P muris* were apparently not examined The results obtained with the mouse-adapted Lansing strain are less consistent It should be pointed out that the activity of the mouse-tissue extracts tested was fairly low; in Levaditi's experiments [28] the unfiltered control material infected only 60%-70% of the inoculated animals Even a slight reduction of the virus-content during filtration would thus bring the concentration in the filtrates below the sensitivity threshold of the method of assay Whether the discrepancies observed can be explained in this way or whether they reflect true differences in particle size in different hosts is at present not clear The same doubt exists with regard to the only filtration experiment on human faecal virus reported Obviously the data given in table I permit only very guarded statements to be made as to the filterability of poliomyelitis viruses

Sedimentation-rate

The sedimentation-rate can be determined either optically on purified material of sufficient concentration to allow of direct observation of the moving boundary, or by biological assay of fractions sampled from different levels of the vessel after termination of a run in the centrifuge In the latter case convection has to be prevented either by the use of a diaphragmed "separation cell" [60] or by the establishment of a density gradient [12] The biological method has the advantage over the optical that the virus need be neither purified nor concentrated Some sedimentation data are given in table II.

With the exception of the observation by Loring & Schwerdt,[36] the figures contained in table II are reasonably uniform The sedimentation-rate of the virus is to a certain extent dependent upon its concentration,

of material for observation in the electron microscope, a method by which even large amounts of impurities may easily be overlooked; the results of these studies are, consequently, not suited to an evaluation of the homogeneity of a preparation.

Size and Morphology

Ultrafiltration

The particle size of a virus can be estimated indirectly by sedimentation and diffusion analysis, by filtration end-point determinations, by light diffraction measurements, by radiation inactivation, and sometimes by x-ray diffraction studies Of these methods filtration is technically much the simplest. In most textbooks the size of the poliomyelitis virus is given as 8-12 mμ, on the basis of filtration experiments by Theiler & Bauer [57] and by Elford et al [8] This value is calculated by means of Elford's empiric formula, according to which the actual particle size in the present size-range should be one third to a half of the pore diameter of a membrane just capable of retaining the virus (filtration end-point) Elford's formula is based upon certain calculated molecular sizes, which were derived from data on sedimentation- and diffusion-rates It is now known that some of the figures on which the formula was based were inaccurate; consequently, its validity is dubious Under these conditions the filtration end-point cannot be used for calculation of the true particle size. It is, on the other hand, a fairly reproducible characteristic and as such of importance as an aid in virus identification

Filterability is best expressed in terms of the limiting pore diameter, that is, the largest pore by which the virus is completely retained This is determined by filtration through a series of membranes with varying pore diameters in combination with activity tests on the filtrates For accurate determinations it is, of course, essential that the intervals between the pore sizes of consecutive membranes in the limiting range should be as narrow as possible For this reason a statement concerning filterability should always include two figures the pore diameter of the densest membrane tested which still permitted the passage of the virus, and the pore diameter of the most porous membrane found to retain the virus. The accuracy of the determination can be evaluated only if these figures are given.

A compilation of data on the filterability of viruses of the poliomyelitis group is contained in table I

The data reveal a satisfactory conformity of results obtained with *P. hominis* type 2 in extracts of infected monkey cord and with the highly virulent strains FA and GD VII of *P. muris* in mouse-brain extracts, the

from the central nervous system, filaments of varying length and with a thickness of about 15 mμ. Similar structures were observed by Melnick [37] The presence of apparently identical filaments in normal non-infectious stools gave rise to the suspicion that they might be flagella detached from intestinal bacteria. Gard [14] later showed that flagella can be prepared in a more or less pure state by methods used in the purification of the virus. Preparations of purified flagella behave in the ultracentrifuge as homogeneous macromolecular substances with sedimentation constants of the same order of magnitude as that of the virus. However, the exact nature of the sedimentable fraction obtained from stools has not yet been established.[17]

Loring et al.[34] published electron micrographs of the purified Lansing rat-brain material previously discussed (see page 219) They found more or less spherical particles with diameters ranging from 12 mμ to 34 mμ. Electron micrographs of more recent years have in general shown similar particles, the sizes of which have been estimated at between 10 mμ and 50 mμ Particles in the same size-range have been found in material derived from normal brain tissue [33, 49, 62] The nature of the objects described is, therefore, not always obvious Thus, in 1949, Rhian et al [49] concluded · " From a critical examination of our work, and that of others, we conclude that there is no evidence that a virus of the poliomyelitis group has ever been unequivocally identified on electron micrographs thus far published "

Since that statement was made some progress has been made

The most convincing results are probably those obtained by Leyon,[30] who studied the FA strain of *P muris* His material was practically homogeneous on sedimentation analysis and had a very high specific activity. Electron micrographs showed as the only visible structures particles of almost perfect spherical shape sometimes arranged in a close-packed hexagonal pattern The diameter was determined as 28 mμ (see fig 1)

Less clear-cut are the results of Kausche & Bender [23] Their material, as judged from its specific activity, was purified to about the same extent as that of Loring et al [34] They found an array of particles of varying size in specimens derived from normal as well as from infected tissue They claim, however, to have been able to single out among these structures spherical particles of about 20 mμ in diameter present only in infectious material

The observations of Reagan et al [47, 48] concern practically crude tissue extracts and the significance of the particles described is, therefore, doubtful

Recently high-quality micrographs of Lansing-type and Brunhilde-type virus showing spherical particles have been released to news magazines and to the daily press by Bachrach & Schwerdt and by a Parke, Davis

TABLE II. SEDIMENTATION STUDIES

Virus	Strain	Origin	Method	s_{20} (Svedberg units)	Reference No
P hominis	Pool	human cord	optical	150	13
	Lansing	monkey cord	optical	83.5	36
	Lansing	mouse brain	biological	195	15
	Lansing	mouse cord	biological	122–170	38
	MEF 1	mouse brain	biological	183	45
P muris	FA	mouse brain	optical	150–181	13
	TO	mouse cord	biological	195	15
	FA	mouse brain	biological	195	15
	FA	mouse brain	optical	151–164	30

which accounts for some of the variation observed. For calculation of the particle size the sedimentation-rate at infinite dilution has to be determined This is usually done by extrapolation to 0 concentration from serial experiments at different concentrations—a safe method only if the sedimentation-rate—concentration relationship is rectilinear. The available data seem to indicate a sedimentation-rate limit in the neighbourhood of $s_{20} = 195$ Svedberg units The question cannot be regarded as definitively settled, however

The particle size cannot be calculated from the sedimentation-rate data unless the particle shape and density are known No density determinations have been carried out However, by combination of sedimentation-rate and diffusion-rate data the particle weight and to a certain extent its shape can be computed The diffusion coefficient of the FA strain was determined by Gard[13] to $D_{20} = 0\ 32 \times 10^{-7}$, from which a particle size of $12\ 5 \times 580$ mμ was calculated On the other hand, Leyon,[30] assuming a spherical shape and a density of the virus of 1 3—approximately that of unhydrated proteins—estimated the particle diameter at about 30 mμ

Irradiation sensitivity

Of other indirect methods for determination of the particle size only the rate of inactivation by ionizing irradiation seems to have been applied Bonét-Maury & Levaditi[3] found that the irradiation-sensitive volume of mouse-adapted Lansing virus corresponded to a particle diameter of about 100 mμ.

Electron microscopy

Electron microscopy offers the possibility of a more direct determination of the size and shape of the virus particle. One of the first attempts by this method was that of Tiselius & Gard;[59] they found, primarily in purified material from infectious stools but also in specimens obtained

from the central nervous system, filaments of varying length and with a thickness of about 15 mμ Similar structures were observed by Melnick.[37] The presence of apparently identical filaments in normal non-infectious

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the electron-microscope screen the shape of spheres, dumb-bells, tailed tadpoles, or short rods, depending upon the salt concentration of the medium from which the specimen is prepared for microscopy The virus seems to be insoluble in the absence of electrolytes, flocculating in the shape of spherical particles, while in the presence of salts it is soluble, assuming a rod shape.[53, 54]

The desiccation necessary in the preparation of a specimen for electron microscopy is known to be harmful to viruses of the poliomyelitis group, damaging not only infectivity but antigenicity as well (see page 226) Whether or not the structure of the virus particle is grossly affected is not known. It appears highly probable that the spherical objects observed by Leyon and by Bachrach & Schwerdt represent the dried virus particles. To what extent they reproduce the morphology of the virus particle in solution, in an active state, is uncertain The close agreement found between filtration end-point and particle diameter as measured on electron micrographs justifies some reserve of judgement Even if Elford's correction formula has to be revised, it is hardly probable that the porosity of the membranes would be completely unaffected by adsorption onto the walls of the pores of soluble substances present in the material to be filtered, that is to say, the effective pore-size on filtration of organic matter should be smaller than the value derived from the pure physical characteristics of the membrane Spheres of the size observed, suspended in a protein-containing fluid, such as a tissue extract, would probably be unable to squeeze through the limiting membranes of 32 mμ average pore-diameter (APD) unless they had a very plastic consistency They may be plastic or the hydrated particles may be elongated, collapsing on desiccation into spheres like the Newcastle virus in an electrolyte-free medium.

Resistance to Physical and Chemical Agents

Chemical nature of the virus

The virus is sometimes referred to as "the virus protein" It is probably true that the poliomyelitis virus, like any other virus that has been examined in this respect, is made up essentially of protein. So far, however, substantial justification for the application of this term is lacking, as no chemical analyses of sufficiently pure preparations have been carried out. The best attempt was made by Leyon,[30] who found that purified *P muris* shows the ultraviolet absorption typical of nucleoproteins.

FIG. 1. ELECTRON MICROGRAPH OF P. MURIS STRAIN FA



Gold-shadowed; magnification x60,000

Reproduced from Leyon et al [31] by kind permission of the editors of *Biochimica et biophysica acta*

& Co team in Detroit, Mich , USA, under the leadership of Taylor. No accounts of the findings in scientific journals have yet been available to the author. Bachrach & Schwerdt apparently used cotton-rat brain as a starting material and, after purification, obtained a homogeneous-infectious fraction of spherical particles, about 25 mμ in diameter Taylor and his associates seem to have started from a tissue culture of Brunhilde, type virus Their micrographs show two distinct types of particle of different sizes

the virus is readily inactivated. Consequently, house dust is not a probable source of virus, nor is airborne infection likely to play a significant part in the epidemiology of poliomyelitis (Faber et al.[9])

Temperature

Like any other protein the virus, on storage, undergoes spontaneous denaturation and inactivation The rate at which this process takes place is determined by environmental factors such as temperature, pH, and the composition of the medium. If the environmental conditions are kept constant, inactivation will proceed at a constant rate; that is to say, in any unit of time the same logarithmic decrease in activity will occur. The rate of inactivation or the half-life time of the virus is, therefore, the most adequate expression of its stability under any given conditions

Unfortunately only a few of the stability studies reported meet the above requirements so that their results are not directly comparable. Leyon,[30] studying the stability of partially purified *P. muris* strain FA, determined the inactivation-rates at different temperatures From his diagrams the half-life time of the virus in phosphate buffer of ionic strength 0 1 and pH 5.1-5.2 can be calculated to approximately 60 minutes at 40°C, 22 5 minutes at 45°C, and 8.5 minutes at 50°C By extrapolation, a half-life time of about 90 seconds at 60°C can be computed

Lépine & Nantel[27] carried out experiments on mouse-adapted Lansing virus They found a temperature—inactivation-rate relationship similar to that observed by Leyon, and reported the inactivation times—that is to say, the time required to reduce the activity to values below the sensitivity threshold of the method of assay—given in the following tabulation ·

Temperature	*Inactivation time*
60°C	6 8 minutes
65°C	2 5 ,,
70°C	1 5 ,,
75°C	50 seconds
80°C	31 ,,

The medium consisted of a 10% brain suspension in physiological saline, pH was not stated As the original titre of their material was not given, the half-life time cannot be calculated from the published data Assuming a titre of about 10^{-3} the half-life time can be estimated at about one tenth of the inactivation time, which agrees reasonably well with Leyon's findings However, the interpretation of their results is complicated by the occurrence of nonspecific mortality among mice inoculated with heated material

The influence of pH on the thermal inactivation-rate has not been studied. Melnick and his associates,[22, 25] however, investigated the protective effect upon the virus of milk and cream Although the results were

Even if the chemical nature of the virus has not been definitely established, a large body of data concerning its physical and chemical properties has been collected Some of these data are of distinctive value for classification purposes, others bear upon the practical problems of disinfection and prevention of dissemination of the virus in society. So far the studies of the in vitro behaviour of the virus concern exclusively the resistance of its biological activities—infectivity and antigenicity—to physical and chemical insults The mechanisms of the effects of the various agents is completely unknown and a rational classification of them is therefore not feasible In the following paragraphs the most important data will be reviewed, and will be classified according to the nature of the active agents rather than according to the mechanism of their action.

Desiccation

It has long been known that lyophilization is a poor method of preservation of poliomyelitis virus activity,[58] a somewhat surprising fact, as freeze-drying has proved of great value in the preservation of a number of viruses of far less general stability than the virus of poliomyelitis Most workers report some residual activity after the lyophilization and reconstitution of virus-containing tissue extracts, usually in the order of magnitude of 1% or less of the original activity Freezing by itself has no deleterious effect On the contrary, the lower the temperature, the higher the stability of the virus It is highly probable, therefore, that the damage is done in the very process of desiccation Why, then, is some residual activity almost constantly observed in lyophilized preparations? One explanation for this may be found in a variation in resistance of the individual virus particles There is, however, another possibility that appears more probable Unless extraordinary measures are taken, lyophilization always leaves some residual moisture in the specimen, often as much as 2% It is, therefore, not unlikely that the residual activity can be accounted for by incomplete desiccation Although this question seems to be of great theoretical interest, no systematic studies have been reported If complete removal of water causes irreversible loss of the infectivity of the virus as well as of its antigenic activity,[43] water molecules must be assumed to enter intrinsically into the structure of the virus particle

The consequences of the sensitivity to desiccation concern not only the laboratory worker but also the public-health officer Desiccation of infected material, such as stools or soiled articles, left to dry at room temperature, is seldom sufficiently complete to ensure inactivation of the virus On the contrary, the medium in which the virus is contained will usually protect it from other inactivating agents, such as oxygen of the air or ultra-violet light. On the other hand, virus containing droplets formed in air of low humidity rapidly develop into droplet nuclei in which

of foot-and-mouth disease by Pyl[46] and for equine encephalitis virus (Eastern strain) by Finkelstein et al [10] So far no definite explanation of this phenomenon has been found

Organic solvents

It has already been indicated that the viruses of the poliomyelitis group are completely resistant to ethyl ether and fairly resistant to methanol and ethanol at low temperatures They are inactivated, although slowly, by acetone,[58] and, more rapidly, by ethylene dioxide. Glycerol seems to exert a preservative effect; residual activity has been reported in specimens stored for eight years in 50% glycerol at 4°C.[50]

Andrewes & Horstmann[1] have found the degree of sensitivity to ethyl ether to be a useful criterion in virus classification The behaviour of a virus in the presence of ether is presumably mainly dependent upon the chemical composition of the virus particle. Viruses which are known to contain considerable amounts of lipids—for example, influenza virus—are momentarily inactivated by ether The poliomyelitis viruses seem to resist completely even a prolonged ether treatment,[55] which suggests that lipids are not essential constituents of the virus particle.

The ethyl-ether test may serve to differentiate the encephalomyocarditis group of viruses from the poliomyelitis group. Viruses in the former group are not completely resistant but are only slowly inactivated by ether, they thus assume an intermediate position between the poliomyelitis group and the highly sensitive encephalitis viruses. Some strains of Coxsackie virus are reported to be ether-sensitive, while the majority are completely resistant

Formaldehyde

The reaction of the virus to formalin is of considerable interest, since Formol-treated virus is being used for purposes of active immunization In spite of the practical importance of this problem, no systematic studies have been carried out. In the formaldehyde-protein reaction, amino groups are primarily involved Each amino group may combine with two molecules of formaldehyde in a reversible, rapidly proceeding reaction Equilibrium is reached within seconds or minutes. The compound dissociates and the formaldehyde can easily be removed by dilution, dialysis, or " neutralization " with bisulfate At an alkaline pH, however, a gradual loss of amino groups may be observed, indicating that secondary irreversible reactions at these sites may occur Apart from this, a number of less well-known processes take place, many of them irreversible and proceeding very slowly [11]

The virus must be assumed to react with formaldehyde in principally the same manner as any other protein, that is to say, reversibly as well

not quite consistent, a certain trend was obvious Thus, while heating for 7.5 seconds at 71.1°C (160°F) destroyed the activity of both the Y-SK strain and the Lansing strain of the virus suspended in water or milk, the virus remained active when suspended in cream for 2 minutes (but not 3 minutes) and 30 seconds (but not 45 seconds), respectively. At lower temperatures a protective effect of milk was demonstrable as well. The authors concluded that the standard method of long-time pasteurization (30 minutes at 61 7°C) gives a reasonable safety margin, but that short-time pasteurization (15 seconds at 71.1°C), on the other hand, while satisfactory in the case of milk, does not ensure complete inactivation of virus in cream It is possible that viruses of different origin, as well as different strains of virus, show differences in stability.

Irradiation

Ionizing irradiation is known to inactivate the virus, although comparatively large doses are needed (see, for example, Bonét-Maury & Levaditi[3]) Likewise ultraviolet light has a definite effect In the studies so far reported different techniques and equipment have been used and the results are not easily comparable By application of suitable methods, however, rapid inactivation can be obtained.[7, 39] On the basis of Leyon's light absorption studies maximum effect might be expected with wavelengths of about 2,760 Å No systematic studies of this question have been carried out

pH stability

The rate of inactivation of *P muris* at different pH was studied by Theiler & Gard[58] on crude tissue extracts and by Leyon[30] on purified material The results were essentially similar, indicating a stability range of from pH 3 to pH 10 Below pH 3 the rate of inactivation increased rapidly but even after several hours at pH 1 5 some residual activity was demonstrable. Above pH 10 the inactivation-rate increased in a similar way According to Leyon, the inactivation-rate at pH 12 and a temperature of 31°C corresponded to about 4 log units in 12 hours.

Similar results were obtained by Loring & Schwerdt[35] with the MVA strain of *P. hominis* After from 15 to 20 minutes at room temperature no inactivation of 1-10 infectious units occurred in the pH range of 1.6-10.3, whereas 10-100 units were inactivated at pH 1 0 or at pH 11 0 In one experiment at pH 11.0 some residual activity was found in a specimen containing originally 100-1,000 infectious units.

As already mentioned (see page 219), the virus, together with about a half of the protein in solution, precipitates from a crude tissue extract in the pH range of 3.5 to 4.5 Theiler & Gard[58] found a stability minimum in the same pH range. Similar findings were reported for the virus

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ammonia or amines a chain of reactions is incited, by which successively mono-, di-, and trichloramines are formed The latter, finally, are oxidized by addition of more chlorine and chlorides appear.

What is called residual chlorine may be either "free" chlorine (Cl_2, hypochlorous acid, or hypochlorite ions) or organically bound (chloramines) *The viricidal activities of these compounds differ considerably:*
[illegible]

easily than the charged ion Lensen et al [28] found a similar pH dependence in the effect upon poliomyelitis virus. The bactericidal action of organically bound chlorine is estimated at only one fiftieth of that of free chlorine Comparable data on the effect upon the virus are lacking; Lensen et al, however, were not able to inactivate the virus at pH 7.0-7 4, temperature 21°C-25°C, and a contact period of 30 minutes with a residual of exclusively organically bound chlorine Free chlorine in a concentration of not more than 0 05 parts per million (p p.m) was sufficient to inactivate the virus under the given conditions

In conclusion, in disinfection of polluted waters the principle of the so-called break-point chlorination has to be observed Most drinking water, however, is almost free from nitrogenous organic compounds and will therefore not present problems of the kind just described. Nevertheless, the practice of adding ammonia to the chlorinated water for the purpose of converting free chlorine into chloramine hardly seems well advised. In this connexion technical problems still awaiting solution are involved.

Iodine is a very effective bactericidal agent and its viricidal power is probably greater than that of chlorine Few systematic studies have been published on the matter Kaiser [21] tested the effect on vaccinia, myxoma, and rabies virus of iodine vapour, generated by bubbling air through an alcoholic solution of iodine Vaccinia virus was inactivated after 30 seconds, myxoma virus after 5 minutes, rabies virus was partially inactivated after 3 minutes Kaiser's experiments do not seem to have led to the development of any practicable methods of disinfection Apart from these experiments, iodine has been used primarily for surface disinfection of the skin As such it is probably vastly superior to any other disinfectant on account of its wide range and rapid action. The alleged importance of injections as precipitating paralytic attacks of poliomyelitis, and the not yet excluded possibility that one of the mechanisms might be implantation of virus deposited on the skin surface, have actualized the use of iodine as

as irreversibly. It is well known that Formol treatment leads to inactivation of the infectivity while the antigenic capacity may be left intact or only partially destroyed [4, 52] The inactivation proceeds comparatively slowly but, in sufficiently high concentrations of formaldehyde, to completion. For this reason it is probable that structures other than amino groups are responsible for the infectivity. The exact chemical nature of inactivation is completely unknown, however.

One factor, often neglected, is that the formaldehyde-binding capacity of a tissue extract or of any other virus-containing material is referable mainly to the presence of non-viral substances. These partly react irreversibly, consuming some of the formalin added, and partly enter into a dissociation equilibrium with it. The end result is a reduction in the concentration of free formaldehyde The presence of impurities thus protects the virus against inactivation [16] For these reasons it is not possible to determine definitively a formalin concentration or a holding period sufficient for complete inactivation of the virus Consequently, treatment with formalin at room temperature is not a reliable method of disinfection. The reaction seems to be highly temperature-dependent, however, and treatment with formaldehyde vapour at 50°C can be recommended for the disinfection of delicate instruments, such as catheters, bronchoscopes, etc

Other disinfectants

Detergents, widely used in bacteriological practice, are without effect on poliomyelitis viruses Phenol inactivates the virus, although slowly and only in comparatively high concentrations [4] Inorganic mercury compounds and many other heavy metals inactivate rapidly and completely [55] Organic mercury compounds, however, such as merthiolate,[4] may be without effect Of more practical importance are different oxidizing agents Ozone is reported to have a rapid effect [24] Potassium permanganate in a concentration of 0 005% inactivated 20 infectious units of virus in two hours [55] Hydrogen peroxide inactivates, but slowly [58]

Chlorine is a good disinfectant when applied correctly Earlier reports on the action of hypochlorite or chloramine were sometimes conflicting One of the reasons for this was unawareness of the role played by nitrogen-containing impurities present in the test material Trask et al [61] studied this question and found not only that much higher doses of hypochlorite or chloramine were required to inactivate the virus in a medium rich in organic material, but also that higher residual chlorine concentrations were needed. Thus, the impurities seemed to act partly by consuming chlorine and partly by affording some kind of special protection against the inactivating agent This peculiar phenomenon is probably explained by more recent findings concerning the mechanism of chlorination.

explanations of their wide dissemination The major part of the virus leaving an infected host is excreted in the faeces, with the result that sewage disposal and water sanitation present certain problems. The virus will remain viable for many months in raw sewage or natural waters, provided the temperature is not too high Unless adequate methods of sewage purification are applied, contamination of rivers, lakes, and other sewage recipients will occur. The problem of water purification has been studied experimentally by Carlson et al,[5] who found that none of the standard methods applied in water sanitation was effective in removing or destroying the virus in heavily polluted water On the other hand, Mundel et al,[41] examining in the course of an epidemic the virus-content of sewage at different stages during its passage through a purification plant, could not demonstrate the presence of virus in digested sludge or in the effluent after sand filtration, although the raw sludge, the settled sewage, and the effluent from humus tanks contained virus This problem needs further clarification

Of the different means by which virus can be inactivated, heating is probably the simplest and most effective Provided that the material to be disinfected is sufficiently dispersed, so that temperature equalization is secured, heating to 60°C for 30 minutes seems to be a reasonably safe method of disinfection Chemical disinfectants are less reliable, mainly on account of the protective effect on the virus exhibited by inert organic matter The pH of the medium is likewise of considerable importance For such reasons no standard procedures of chemical disinfection can be recommended

One of the purposes of the present review has been to direct attention to some of the controversial and insufficiently studied subjects of theoretical and practical importance in the field of experimental poliomyelitis research With the new tools now available the solution of many of the problems here discussed are within reach It is to be hoped that this article will be out of date in a few years' time

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a skin disinfectant in preparation for injections. It can only be stated that, as a means of removing or inactivating virus on the skin, the use of soap, detergents, ether, ether-alcohol, or chloramine is nothing but a symbolical ritual; only iodine might be expected to serve the purpose.

Miscellaneous substances

In the search for inactivating agents to be used as disinfectants or for therapeutic purposes, a great number of substances have been tested more or less at random. One of the more ambitious efforts was that of Schultz & Robinson[65] who screened no less than 112 different agents Among those tested a few proved viricidal in concentrations of 0.1% or less, namely, chrysoidin Y, Congo red 4 B, copper sulfate, hexylresorcinol, mercuric chloride, Mercurochrome, methylene blue, oxyquinoline sulfate, potassium hydroxide, and potassium permanganate Some of these have already been discussed. Nitrogen and sulfur mustards also have a definite inactivating effect[66]

General Conclusions

A double purpose is served by in vitro studies of the poliomyelitis virus The virologist in the laboratory wants information about the nature of the virus in order to be able to identify it and to obtain some insight into the mechanism of the interaction between the virus and the cell The field worker—the clinician and the public-health officer—need means and methods by which the virus can be destroyed and its dissemination prevented. Admittedly little advance has been made in either connexion

The immunological criteria are still the only reliable ones by which poliomyelitis viruses can be identified Of the diverse physical and chemical properties which have been discussed, few are fully established and none are really distinctive The most valuable ones seem to be ether-resistance and filterability The former property is not unique, the poliomyelitis group shares it with several other viruses, some not even remotely related. If, however, a virus strain should be isolated which possessed biological characteristics compatible with those of a poliomyelitis virus, but which was sensitive to ethyl ether, one would hesitate to label it a *Poliovirus* The filtration end-point might be a more specific characteristic. In this respect, however, knowledge is still insufficient A third property that might carry some significance from a classification point of view is sensitivity to desiccation This phenomenon also requires further study.

Generally speaking, the viruses of the poliomyelitis group are among the hardiest of all known animal viruses This is probably one of the

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THE PRESENT PLACE OF VIRUS LABORATORY TESTS IN THE DIAGNOSIS OF POLIOMYELITIS

With Special Reference to Tissue-Culture Techniques *

A. J. RHODES, M.D., F.R.C.P. (Edin.)

Director, Research Institute,
The Hospital for Sick Children, Toronto

Professor of Virus Infections,
School of Hygiene, University of Toronto, Ontario, Canada

W. WOOD, M.B., B.S.

Research Associate,
Connaught Medical Research Laboratories,
University of Toronto, Ontario, Canada

DARLINE DUNCAN, B.A.

Research Assistant,
Research Institute, The Hospital for Sick Children,
Toronto, Ontario, Canada

Introduction

The clinical features of poliomyelitis are also those of various other diseases, and some difficulty may therefore be experienced in establishing an accurate diagnosis. The problem of differential diagnosis is most acute in the abortive and the meningitic (non-paralytic) forms of poliomyelitis, for several bacterial and virus infections have similar clinical features. Virus infections which simulate these forms of poliomyelitis include [illegible]
Coxsacki [illegible]
and lym [illegible]
pyogenic [illegible] ...culous, as well as leptospirosis, must sometimes be considered in the differential diagnosis.

* Contribution from Department of Paediatrics, University of Toronto, Research Institute, The Hospital for Sick Children, Toronto, and Connaught Medical Research Laboratories, University of Toronto, Ontario, Canada.

Collection and Preparation of Specimens for Isolation of Poliomyelitis Virus *

In fatal cases, attempts may be made to isolate poliomyelitis virus from suspensions of brain or spinal cord, or from colonic contents; histological examination of the central nervous system should also be carried out. In non-fatal cases, stools represent the most suitable specimen; if necessary, a plain water enema may be administered in order to obtain a specimen. Throat swabbings or gargling may also be tested. In view of current interest in viraemia, many workers will probably wish to examine whole blood (oxalated) for the presence of virus, although positive results are unlikely with specimens collected after the onset of symptoms.[9, 26]

Specimens should be stored temporarily in a refrigerator (0°C-4°C) pending submission to the virus laboratory. In the event that early delivery or shipment is impracticable, specimens (except whole blood) should, if possible, be placed in an electric "deep-freeze" or carbon-dioxide-ice chest. Later, shipment of frozen specimens may be made in a suitable container with carbon-dioxide ice. In our experience, it is adequate to ship specimens for poliomyelitis diagnosis in containers cooled with "ordinary" ice. On receipt in the virus laboratory, specimens are usually stored frozen until tests can be carried out. For storage, electric "deep-freezes" of the types available for domestic use are very satisfactory.

The advent of antibiotics has greatly simplified the technical methods of isolating poliomyelitis virus. Suspensions of nervous tissue, or throat swabbings or washings, are treated with penicillin (500 units per ml) and streptomycin (250 μg per ml) and are then ready for inoculation. Stools can be prepared in various ways. Undoubtedly, the best method is to prepare extracts by ultracentrifugation in the Spinco high-speed centrifuge (see Annex 2, page 260). However, it is not necessary to prepare stools by this method; simple etherization of a lightly clarified watery suspension is adequate. In the preparation of stools, also, the final suspension should be treated with antibiotics. In epidemiological surveys, where it is desired to examine the stools of large numbers of persons, it is common practice to prepare individual suspensions and to "pool" these before inoculation. Recently, a method of concentrating such specimens before pooling has been described.[20]

Until quite recently, suspensions of pathological specimens so prepared were routinely inoculated in monkeys, but tissue cultures are being increasingly used and are to be recommended.

* The first report of the WHO Expert Committee on Poliomyelitis[14] provides in Annex 1 detailed instructions for the collection, storage and shipment of specimens. This Annex is reprinted as Annex 1 to the present contribution (see page 253). It should be consulted for detailed information.

In regard to the paralytic form of the disease, difficulty may be experienced in differentiating between poliomyelitis and the Guillain-Barré-Landry syndrome, especially as *this syndrome is now defined in wide* terms[24] The diagnosis of the less severe forms of bulbar poliomyelitis may likewise present difficulties

Some interest has been aroused by a number of reports of poliomyelitis-like illnesses, apparently not caused by any known agent. These reports, from Iceland,[48] Australia,[37] and North America (D White, Kingston, Ontario—personal communication, 1953) refer to syndromes characterized by the presence of muscle tenderness, paresis, and psychological complications

In view of these difficulties in diagnosis, it is reasonable to inquire whether the virologist is in a position to assist the clinician, and it is the object of this contribution to indicate the help that may be expected from virus diagnostic tests

Tests for the laboratory diagnosis of poliomyelitis fall into three main groups "direct" tests for the presence of poliomyelitis virus in pathological specimens, "indirect" or serological tests for the presence of poliomyelitis antibody in patients' blood; and, thirdly, tests for the presence of other viral or bacterial agents

One of us (A J R) has been engaged in a study of certain aspects of this problem in Toronto for some years,[39] and more recently with his associates has had experience in the use of tissue-culture methods for the diagnosis and study of poliomyelitis[16 18, 19] This contribution has been prepared in the light of such experience, and main attention will be paid to the use of tissue-culture methods, for the introduction of these newer techniques has rendered obsolete most of the traditional methods of isolation and serological examination by animal inoculation.

It will not be possible to enter into a description of the methods to be followed to establish a positive diagnosis of the various infections that simulate poliomyelitis, as such a description would have to cover much of the field of diagnostic virology Relevant discussion will be found in various texts[1, 25 39 41, 55] In general terms, it may be said that examination of the cerebrospinal fluid by simple film and biochemical tests seldom provides information of much help in the differential diagnosis of the various causes of virus meningitis. Cell counts in poliomyelitis tend to be lower than in other forms of virus meningitis, but there are wide variations from case to case Bacteriological and biochemical tests are, of course, invaluable in the diagnosis of pyogenic and tuberculous meningitis

Typing of Poliomyelitis Virus Strains in Monkeys

Approximately 200 strains of poliomyelitis virus have been typed by the Committee on Typing of the National Foundation for Infantile Paralysis, Inc., New York, USA.[34, 35, 47] This work was initiated before tissue-culture methods were generally available, and was therefore conducted by monkey inoculation. Various technical methods were followed, but the most generally acceptable was one introduced by Salk et al.,[46] in which suspensions of the strain to be typed, mixed with paraffin oil adjuvant, *were inoculated intramuscularly in monkeys on two or more occasions.* The serum of the immunized animals was tested by the virus-neutralization technique for antibody to the three prototype strains; these tests were carried out by monkey inoculation.

Recently, several laboratories have typed additional strains of poliomyelitis virus in tissue cultures, and there is no doubt that further studies will be carried out by this technique (see page 246). The inoculation of tissue cultures represents the only method whereby considerable numbers *of strains can be typed for a reasonable expenditure of time and money.*

Methods of Passage of Poliomyelitis Virus in Rodents and Chick Embryos

The original adaptation of the Lansing strain of poliomyelitis virus to rodents was made by Armstrong,[2, 3] and other type 2 strains have since been adapted.[4] More recently, it has been reported that all three types of virus have been adapted to mice by a technique requiring intraspinal injection.[22, 28, 29, 30] The inoculation of rodents is not, however, recommended for general use in diagnostic laboratories. Type 2 viruses are very rare causes of epidemic poliomyelitis. Furthermore, the fact that many *rodents carry viruses of the encephalomyelitis or encephalomyocarditis* groups may lead to serious errors in the interpretation of results.

Type 2 virus has been successfully adapted to chick embryos.[30, 33, 43] Nevertheless, the inoculation of chick embryos would not seem to have a place in the routine laboratory diagnosis of poliomyelitis.

Isolation and Identification of Poliomyelitis Viruses in Tissue Cultures

Pathological specimens for inoculation into tissue cultures should be collected as previously mentioned (see also Annex 1, page 253). *Inocula* are prepared as described, and it is important to note that antibiotics must be added. Stool suspensions may be prepared by etherization, but

Isolation and Identification of Poliomyelitis Virus in Monkeys [b]

Until quite recently, inoculation of monkeys represented the only means whereby a strain of poliomyelitis virus could be isolated and identified. Most work has been done with the Indian rhesus monkey or the cynomolgus monkey from the Philippine Islands In the tropics, readily available local species may be used Chimpanzees have been employed in studies on immunology and pathogenesis, but are too costly for diagnostic work. Monkeys which are to be used in poliomyelitis diagnosis should look healthy, be free from diarrhoea, and give a negative response to inoculation of tuberculin in the upper eyelid (0 1 ml of 1/100 Old Tuberculin)

Specimens prepared as previously outlined are inoculated intracerebrally, by the technique described by Bodian, Morgan & Schwerdt [8] in which 0.5 ml is injected in each thalamus When larger amounts of inoculum are available, 5-20 ml may also be inoculated intraperitoneally If, for any reason, the proposed inoculum contains large numbers of bacteria, repeated intranasal instillation may be employed as an alternative

Following inoculation, the animals are allowed to run around the animal room once or twice daily, so that paralysis may be the more readily detected Rectal temperatures may be taken, but this is a time-consuming procedure and is probably unnecessary in diagnostic work The animals are usually killed as soon as paralysis is definitely observed Portions of the cortex, thalamus, mid-brain, medulla, and spinal cord enlargements are taken for histological examination Animals that do not develop paralysis are killed after 28 days It is highly desirable that a diagnosis of poliomyelitis infection by monkey inoculation, whether positive or negative, should be based on the results of histological examination. It is particularly important that a histological examination should be performed when a monkey has remained clinically healthy, as lesions of subacute poliomyelitis are not infrequently found in the central nervous system of inoculated monkeys

Tissue-culture methods have very largely replaced monkey inoculation for the direct isolation of poliomyelitis virus Nevertheless, and especially in parts of the world where monkeys are locally abundant and cheap, monkey inoculation still represents the simplest method of isolating virus Laboratories able to isolate strains of virus in monkeys can transmit such strains for identification and antigenic typing to a centre where tissue-culture methods are employed Such a procedure has been recommended in the first report of the WHO Expert Committee on Poliomyelitis (see page 36 of the committee's report [59]).

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[b] The methods to be followed in the isolation of poliomyelitis virus by the inoculation of monkeys are given in detail in Annex 1 (page 253).

containing antibiotics, and are then minced with scissors until the fragments measure about 1 mm in diameter These fragments are washed twice before use. The fluid used during the mincing process and for washing is Mixture No. 199 with antibiotics

At the moment, most workers prepare cultures with tissue from freshly obtained organs Certain alternatives have, however, been explored The University of Minnesota (Minn , USA) group has recommended the use of a strain of cells (HeLa) derived from a cervical carcinoma [47] These cells can be propagated indefinitely in the form of stock cultures in the laboratory A human fibrosarcoma strain of cells has also been used [51] Other workers report on the successful cultivation of human cells [4 5 51] It would appear, however, that freshly obtained organs represent the most reliable source of tissue for cultures, and are to be recommended to laboratories entering this field for the first time

Nutrient media

On account of the interest shown in synthetic nutrient media in Toronto, we have for some years had ready access to supplies of Mixture No 199 elaborated by Morgan, Morton & Parker [52] This mixture can be prepared on a relatively small scale (see Annex 4, page 262), or on a much larger scale for the production of substantial quantities of virus-infected fluids Mixture No 199, without addition of serum, has been used in our laboratory in all aspects of the study of poliomyelitis virus, and is a satisfactory nutrient Nevertheless, the addition of normal horse serum (0 5%-5%) ensures a more luxuriant growth of cells Mixture No 199 without horse serum is used for flask cultures, and for fluid changes of roller cultures in which cell growth has occurred Mixture No 199 plus horse serum is preferred to initiate cell growth in roller cultures Penicillin, 500 units, and streptomycin, 250 µg, are added per ml of nutrient at the time of preparation

We have also had experience in the use of nutrient media containing serum ultrafiltrate, chick- or beef-embryo extract, and horse serum A mixture that we have used is composed of three parts of Hanks' balanced salt solution and one part of Simms' ox-serum ultrafiltrate, with the addition of 2 5% beef-embryo extract, 10% normal horse serum, and antibiotics. It is probable that a mixture such as this, or one of the mixtures described by Enders,[d] is to be preferred for use in laboratories unable to prepare or obtain Mixture No 199

It should of course be noted that for certain purposes—such as studies on the physical properties and chemical structure of the virus, studies on virus inhibitors, and for the preparation of a vaccine—it is essential to

[d] See page 269

we would recommend ultracentrifugation whenever possible (see Annex 2, page 260).

Inasmuch as another contribution to this monograph [e] describes general technical methods in tissue culture, main attention will be given in the following paragraphs to methods which have been well tried in our laboratories in Toronto during the past three years and which have become routine procedures. The needs of diagnostic laboratories in hospitals or public-health organizations will be specially borne in mind. Attention is drawn to the valuable monograph of Parker [36] on technical methods of tissue culture.

Preparation of glass-ware

We make a practice of treating glass-ware with concentrated acid wherever possible to ensure removal of all organic matter. Our present procedures are given in detail in Annex 3 (page 260). Many laboratories do not use this rigorous treatment of glass-ware, and appear to obtain satisfactory results by the use of chemical detergents followed by numerous rinsings Nevertheless, when synthetic nutrients are employed, glass-ware must be of the highest degree of cleanliness

Tissues

The choice of tissues will depend on local circumstances. In some areas, human embryos can be obtained readily and frequently; such embryos should be employed only if they are in a healthy-looking condition and show no sign of maceration In our experience, the best results are obtained if embryos are collected from the operating room as soon as possible, and are then immediately minced finely in the laboratory Cultures can be set up some hours later, if necessary Embryonic skin and muscle tissues, finely minced, are very suitable for roller-tube cultures, for flask cultures, the minced tissues of the whole embryo may be employed. Human tonsil is readily available in most hospitals, and we have employed this tissue successfully in flask cultures [19] Tonsillar tissue may also be used in roller tubes, as a source of fibroblasts.[4, 5] Uterus may be used as a source of fibroblasts in roller-tube cultures

We have had most experience in the use of monkey tissue Kidney tissue is used for flask cultures, and either kidney or testis for roller cultures. With kidney cultures, the cellular growth is mainly epithelial, and with testis, mainly fibroblastic

Human or monkey tissues are prepared for flask or roller cultures in a similar fashion The organs are washed several times in nutrient fluid

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[e] See contribution by J F. Enders on page 269.

containing antibiotics, and are then minced with scissors until the fragments measure about 1 mm in diameter. These fragments are washed twice before use. The fluid used during the mincing process and for washing is Mixture No 199 with antibiotics

At the moment, most workers prepare cultures with tissue from freshly obtained organs. Certain alternatives have, however, been explored The University of Minnesota (Minn , USA) group has recommended the use of a strain of cells (HeLa) derived from a cervical carcinoma [47] These cells can be propagated indefinitely in the form of stock cultures in the laboratory A human fibrosarcoma strain of cells has also been used [51] Other workers report on the successful cultivation of human cells.[4, 5 54] It would appear, however, that freshly obtained organs represent the most reliable source of tissue for cultures, and are to be recommended to laboratories entering this field for the first time

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It should of course be noted that for certain purposes—such as studies on the physical properties and chemical structure of the virus, studies on virus inhibitors, and for the preparation of a vaccine—it is essential to

[a] See page 269

employ a medium the composition of which can be strictly reproduced from batch to batch, and which does not contain animal proteins.

Preparation of flask cultures

Two drops of a suspension of minced monkey kidney or other tissue are added from a large-bore Pasteur pipette to 3 ml of Mixture No. 199 (without horse serum) in a 25-ml Erlenmeyer flask. The approximate weight of tissue in 3 ml of fluid is 30 mg. The flasks are stoppered with white non-toxic rubber stoppers [e] and incubated at 37°C overnight The following day, the nutrient is replaced with fresh fluid, and the flasks are ready for inoculation with specimens as described in a later paragraph.

Preparation of roller-tube cultures

One drop of reconstituted chicken plasma is spread evenly over the lower third of a chilled, rimless, Pyrex test-tube (150 mm × 16 mm). Four fragments of minced monkey testis, monkey kidney, or human embryonic tissue are embedded on the plasma-lined area. One drop of reconstituted chick-embryo extract is added and the tube is rotated until the plasma clots. One ml of Mixture No 199 containing horse serum is added, and the tubes are stoppered with white rubber stoppers. They are then rotated at about 12 revolutions per hour in a mechanically driven drum [f] at 37°C for from 5 to 7 days. No change of medium is made during this period At the end of this time, cultures showing a satisfactory outgrowth of fibroblasts or epithelium are selected for inoculation with pathological specimens. A number of workers have now dispensed with rotation during the phase of cell proliferation. Rotation is, however, desirable after the addition of virus

Isolation of viruses from pathological specimens

Two methods can be used for the isolation of viruses from pathological specimens In the first method, reconstituted ultracentrifuged deposit of stool (0 1 ml), or a suitable suspension of other specimen, is inoculated in each of two or more flask cultures of monkey kidney or human embryonic tissue (fig 1). In each group, six additional cultures to which no stool extract is added serve as controls. Cultures are incubated for four weeks, and changes of fluid are made twice weekly. The pH of the cultures is read by visual comparison with pH standards in similar flasks. The readings are made by the same worker under similar conditions immediately before each change of fluid The presence of poliomyelitis virus is suggested if

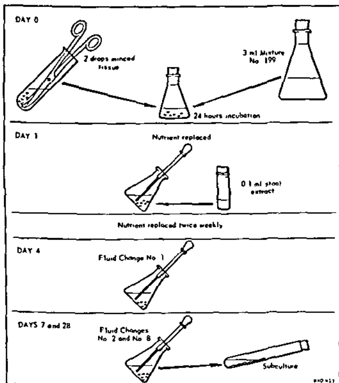
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[e] Obtainable from The West Company, Phoenixville, Pa. USA

[f] Obtainable from Wyble Engineering Development Corp , Silver Spring, Md. USA

the pH remains unaltered or little affected during the later stages of the culture. Fluid is removed at fluid changes 2, 4, 6, and 8, and frozen.

FIG. 1. PRIMARY ISOLATION OF POLIOMYELITIS VIRUS IN FLASK CULTURES



A quantity of 0 1 ml of fluid changes 2 and 8 is inoculated into each of a group of three roller-tube cultures, which are examined daily for cytopathogenic changes If the cells remain normal, the nutrient is replaced after seven days , the cultures are observed for an additional seven days, after which time they are discarded, if there are still no degenerative changes If degeneration is noted, the fluid is removed immediately This fluid is subcultured into a group of five roller-tube cultures which are again examined daily for evidence of the cytopathogenic effects. As soon as degeneration is observed, fluids are removed and stored frozen , fluids from several cultures may be combined to serve as " virus pools"

The main advantage of this first method is that the non-specific cytotoxic effect exhibited by many stool suspensions is diluted during the fluid

changes in the flask cultures By the time subinoculation into roller-tube cultures takes place, this non-specific factor has been removed

In the alternative method, roller tubes are inoculated directly with stool suspension In our experience, this usually leads to pronounced non-specific degeneration in the cells However, if repeated transfer of the fluid elements of the cultures is made, this non-specific factor is eventually removed. We have isolated several strains by this second method. Enders[9] has described a procedure for reducing the non-specific cytotoxic action of stool suspensions

Identification and typing of viruses

In the routine identification of virus pools prepared as described, it is not necessary to carry out a titration in tissue culture One volume of a 1/2 dilution of the tissue-culture virus pool is mixed with an equal volume of a 1/10 dilution of each of the following sera (*a*) normal rhesus monkey serum; (*b*) type 1 monkey poliomyelitis antiserum; (*c*) type 2 antiserum, (*d*) type 3 antiserum These mixtures are left at room temperature for 1½ hours, and 0.1-ml volumes are then inoculated into groups of five roller-tube cultures The final readings are made on the seventh day after inoculation. The type of the virus strain is indicated by inhibition of the cytopathogenic effect in the presence of one of the three type-specific sera When kidney cultures are used, the results of the typing test may be evident as early as 48 hours after the addition of the virus-serum mixtures When testis cultures are used, the results are generally not clear-cut until 96 hours have elapsed

Potent immune sera are prepared by the intramuscular injection of monkeys every 10-14 days with 2 ml of a mixture of live virus, prepared in tissue culture, and Freund's paraffin oil adjuvant as recommended by Salk et al[46] Neutralization titres greater than $10^{-3.0}$ are usually found in serum obtained 5-6 weeks after the start of the immunization programme, and titres of over $10^{-5.0}$ are not uncommon. The 50% neutralization titres of sera used for typing should not be below $10^{-3.0}$, and should preferably be $10^{-4.0}$.

To date, we have typed in tissue culture 100 cytopathogenic strains isolated from cases of poliomyelitis in Canada from 1948 to 1953. The distribution according to types is as follows: type 1 poliomyelitis virus, 82 strains; type 2, 2 strains; type 3, 6 strains; untypeable, 10 strains.

Agents resembling poliomyelitis virus in tissue culture

We have isolated from stools 10 agents which produce cytopathogenic changes in tissue culture, but which are not inhibited by any of the three

9 See page 287

poliomyelitis immune sera It is possible that this result could be produced by a poliomyelitis virus of very high titre, such an agent should be titrated A mixture of more than one type of poliomyelitis virus could produce a similar effect. For titration, dilutions of the tissue-culture fluid in "half-log" steps are prepared with a separate pipette for each dilution Dilutions of $10^{-3.0}$ to $10^{-7.0}$ are inoculated (0 1-ml amounts), together with 0 9 ml of Mixture No. 199, into groups of five roller-tube cultures Five control cultures receive 1 ml of fresh Mixture No 199 only The tubes are rotated at 37°C, and the final reading is made after seven days The titres are expressed as 50% cytopathogenic doses (CPD_{50}) or 50% tissue-culture doses (TCD_{50}) calculated by the Kärber method

The typing test is then repeated with 100 CPD_{50} of the untyped agent and the three immune sera If the agent still causes cytopathogenic changes in the presence of the antisera, it is concluded that it does not belong to any of the three known types Monkeys and suckling and adult mice are then inoculated to test for pathogenicity, and the cornea of the rabbit is also inoculated. If these tests are negative, the agent is classified as "unidentified"

The significance of agents of this type cannot be evaluated at the present time, and further work is necessary Similar findings have been reported by others,[40, 49, 56] it is of particular interest to note the isolation by Steigman and his associates of one of these agents from human spinal cord

Monolayer cultures

Recently, Dulbecco has introduced a technique in which cells are cultivated in a single layer, and has found that the virus of Western equine encephalomyelitis produces plaques on such "monolayer" cultures of chick-embryo tissue[14] He has also shown that similar plaques develop in monolayer cultures of monkey testicular and kidney cells infected with poliomyelitis virus[15] Youngner[60] has modified this technique, and has studied the effect of poliomyelitis virus on monolayer cultures of monkey kidney in roller-tubes, this technique was demonstrated recently to one of us (W W), and it has since been adopted as a standard procedure for the assay of virus and the titration of antibody Observations suggest that these monolayer cultures are several times more sensitive to the presence of virus than are cultures prepared from fragments of monkey kidney as previously described

Serological Methods in the Diagnosis of Poliomyelitis

Two antibodies can be recognized in poliomyelitis infections: the virus-neutralizing antibody and the complement-fixing antibody. Of the

changes in the flask cultures. By the time subinoculation into roller-tube cultures takes place, this non-specific factor has been removed.

In the alternative method, roller tubes are inoculated directly with stool suspension. In our experience, this usually leads to pronounced non-specific degeneration in the cells However, if repeated transfer of the fluid elements of the cultures is made, this non-specific factor is eventually removed We have isolated several strains by this second method. Enders[f] has described a procedure for reducing the non-specific cytotoxic action of stool suspensions

Identification and typing of viruses

In the routine identification of virus pools prepared as described, it is not necessary to carry out a titration in tissue culture. One volume of a 1/2 dilution of the tissue-culture virus pool is mixed with an equal volume of a 1/10 dilution of each of the following sera . (*a*) normal rhesus monkey serum , (*b*) type 1 monkey poliomyelitis antiserum ; (*c*) type 2 antiserum , (*d*) type 3 antiserum These mixtures are left at room temperature for 1½ hours, and 0.1-ml volumes are then inoculated into groups of five roller-tube cultures The final readings are made on the seventh day after inoculation The type of the virus strain is indicated by inhibition of the cytopathogenic effect in the presence of one of the three type-specific sera When kidney cultures are used, the results of the typing test may be evident as early as 48 hours after the addition of the virus-serum mixtures. When testis cultures are used, the results are generally not clear-cut until 96 hours have elapsed

Potent immune sera are prepared by the intramuscular injection of monkeys every 10-14 days with 2 ml of a mixture of live virus, prepared in tissue culture, and Freund's paraffin oil adjuvant as recommended by Salk et al[46] Neutralization titres greater than $10^{-3.0}$ are usually found in serum obtained [illegible]
and titres of over [illegible]
of sera used for ty[illegible]
be $10^{-4.0}$

To date, we have typed in tissue culture 100 cytopathogenic strains isolated from cases of poliomyelitis in Canada from 1948 to 1953. The distribution according to types is as follows: type 1 poliomyelitis virus, 82 strains, type 2, 2 strains; type 3, 6 strains; untypeable, 10 strains.

Agents resembling poliomyelitis virus in tissue culture

We have isolated from stools 10 agents which produce cytopathogenic changes in tissue culture, but which are not inhibited by any of the three

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[f] See page 287

poliomyelitis immune sera. It is possible that this result could be produced by a poliomyelitis virus of very high titre; such an agent should be titrated. A mixture of more than one type of poliomyelitis virus could produce a similar effect. For titration, dilutions of the tissue-culture fluid in "half-log" steps are prepared with a separate pipette for each dilution. Dilutions of $10^{-3.0}$ to $10^{-7.0}$ are inoculated (0 1-ml amounts), together with 0 9 ml of Mixture No 199, into groups of five roller-tube cultures Five control cultures receive 1 ml of fresh Mixture No 199 only The tubes are rotated at 37°C, and the final reading is made after seven days The titres are expressed as 50% cytopathogenic doses (CPD_{50}) or 50% tissue-culture doses (TCD_{50}) calculated by the Kärber method

The typing test is then repeated with 100 CPD_{50} of the untyped agent and the three immune sera. If the agent still causes cytopathogenic changes in the presence of the antisera, it is concluded that it does not belong to any of the three known types Monkeys and suckling and adult mice are then inoculated to test for pathogenicity, and the cornea of the rabbit is also inoculated If these tests are negative, the agent is classified as "unidentified"

The significance of agents of this type cannot be evaluated at the present time, and further work is necessary Similar findings have been reported by others,[40, 49, 56] it is of particular interest to note the isolation by Steigman and his associates of one of these agents from human spinal cord

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Serological Methods in the Diagnosis of Poliomyelitis

Two antibodies can be recognized in poliomyelitis infections: the virus-neutralizing antibody and the complement-fixing antibody. Of the

two, the virus-neutralizing antibody has been studied by far the more intensively.

Virus-neutralization tests in monkeys

Until the general introduction of tissue-culture methods, neutralizing antibody to types 1 and 3 poliomyelitis virus could be studied only by the inoculation of virus-serum mixtures in monkeys. The earlier literature contains many references to such tests but, as a rule, insufficient numbers of animals were employed for the neutralizing end-point of the serum to be estimated accurately.

More recent workers have used larger numbers of animals, and serum end-points have accordingly been estimated more accurately. Reference may be made to the extensive use of virus-neutralization tests in monkeys during the programme of typing 200 strains of virus carried out by the Committee on Typing of the National Foundation for Infantile Paralysis, Inc , New York, USA. Although these tests were not employed to study antibody responses in patients, the general technical methods used are applicable. Studies on virus-neutralizing antibodies in poliomyelitis patients were carried out by Hammon & Roberts [23] and by Steigman & Sabin [50] who demonstrated a rise in antibody if the acute-phase sample was taken very early in the illness This early rise in antibody, which probably brings to an end the period of viraemia, is characteristic of poliomyelitis infection in man [7]

In our experience, even in a community where physicians and the lay public are very familiar with the clinical features of poliomyelitis, it is unusual for patients to be admitted to hospital sufficiently early in their illness for virus-neutralization tests to prove of much value in diagnosis

We do not believe that it is necessary for further tests for virus-neutralizing antibody to be carried out in monkeys; these tests should now be performed in tissue cultures

Virus-neutralization tests in mice

A considerable volume of work has been done on the virus-neutralization test in mice in which the Lansing or MEF 1 (type 2) strains are employed, and valuable information regarding the basic immunology of poliomyelitis in various parts of the world has been accumulated. However, inasmuch as type 2 virus is a rare cause of epidemic poliomyelitis, this antibody test has virtually no value as a diagnostic aid.

It would appear that the type 2 antibody test, carried out by conventional methods in mice, should, like the corresponding tests for type 1 and type 3 antibody in monkeys, be considered obsolete. Those who are anxious

to carry out such tests, for some particular reason, should use the standard procedure described in full in Annex 2 to the first report of the WHO Expert Committee on Poliomyelitis (see page 56 of the committee's report [89]) Future studies should be conducted by the tissue-culture technique although, if the claims of Li & Schaeffer, mentioned previously (see page 241), are widely confirmed, intraspinal inoculation of mice may afford a useful alternative technique.

Virus-neutralization tests in tissue cultures

There is no doubt that the tissue-culture technique represents the ideal method of testing serum for the presence of antibody, and a number of interesting papers on the subject have already appeared. For example, Melnick & Ledinko [81] were able to calculate the ratio of inapparent to clinical infections in a population group. Salk [45] used the test in his studies on the antigenicity of a tissue-culture poliomyelitis vaccine. We ourselves have used this technique in a serum survey of an Eskimo population [88] A description of the technical methods used in our laboratories follows.

An acute-phase serum, taken not more than three days after the onset of the disease, and a convalescent-phase serum, taken approximately one month later, are required for the test Serum samples should be either stored in the refrigerator or, preferably, frozen while awaiting test

Dilutions of the serum to be tested are made in Mixture No 199 or sterile saline, with a separate pipette for each dilution Dilutions may be tenfold, but should preferably be twofold To these dilutions are added equal volumes of each of the three standard viruses (for example, type 1, Mahoney, type 2, MEF 1, type 3, Saukett) diluted so that every 0.1 ml of the virus-serum mixtures contains 100 CPD_{50} of virus These virus-serum mixtures are allowed to stand at room temperature for 1½ hours, and are then inoculated into groups of five roller-tube cultures (0 1 ml per tube) At the same time, the three standard viruses are titrated by inoculating appropriate "half-log" dilutions into groups of five roller-tube cultures From these titrations of virus, it may be determined whether 100 CPD_{50} of the standard-type viruses have in fact been added The final reading of both the serum and the virus titrations is made after seven days, and the titre of the serum is expressed as the 50% cytopathogenic inhibiting dose ($CPID_{50}$), and is calculated by the Kärber method

Demonstration [illegible]
one of the type [illegible]
in question was [illegible]
the absence of [illegible]
performed with [illegible] the patient

The result of tests with the sera of a boy aged five years, admitted to The Hospital for Sick Children, Toronto, in 1952 with paralytic poliomyelitis may be quoted ; a significant antibody rise to the Mahoney strain was noted, and type 1 virus was isolated from the stool :[h]

	$CPID_{50}$ titre against type 1	type 2	type 3
Acute-phase serum (3 days after onset of disease)	1 7	2 5	0 3
Convalescent-phase serum (35 days after onset of disease)	3 5	1.5	0

Such an examination affords the strongest proof available in non-fatal cases that the illness in question was in fact poliomyelitis.

Complement-fixation test

Complement-fixing antigens can be prepared by two methods In *the first method, type 2 antigen is prepared from the brains of suckling* mice[11, 12, 13, 27, 45] Of more general value are antigens prepared for all three types of virus grown in tissue culture[52, 53] It seems that, like the virus-neutralizing antibody, complement-fixing antibody also appears in the serum very early in the course of the disease, and soon reaches peak titre. If this finding is substantiated in further studies, it does not appear likely that the complement-fixation test will prove more useful than the neutralization test in the diagnosis of poliomyelitis The complement-fixation test may, however, prove to be a valuable tool in serum surveys, as a positive test probably indicates a comparatively recent infection[21]

Discussion

The object of this contribution has been to describe the diagnostic aids that may be offered by the virus laboratory to the clinician faced with problems in the diagnosis of poliomyelitis The tests available include direct tests for the presence of poliomyelitis virus in the central nervous system, throat secretions, stools, and possibly blood Additional assistance may be afforded by a virus-neutralization or complement-fixation test with acute-phase and convalescent-phase serum.

The isolation of poliomyelitis virus from pathological specimens of a patient suffering from an illness clinically resembling poliomyelitis justifies a tentative diagnosis of this disease The diagnosis is rendered considerably more likely if homologous or homotypic virus-neutralizing antibody

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[h] This boy showed a transitory increase in type 2 antibody as described by Sabin.[44]

develops during convalescence Further support is afforded for a diagnosis of poliomyelitis if tests for the presence of other infections prove negative. In our experience, primary mumps meningitis is one of the most common causes of a virus meningitis resembling poliomyelitis. We also believe that Coxsackie virus is a common cause of virus meningitis resembling poliomyelitis[17] Accordingly, we recommend that, wherever possible, a mumps serum complement-fixation test and an examination of stools for Coxsackie virus should be performed in cases of suspect non-paralytic poliomyelitis.

It must be realized that an indisputable diagnosis of poliomyelitis can be made only if the case proves fatal, on the basis of characteristic neuro-histology and of virus isolation For practical purposes, however, if poliomyelitis virus is recovered from a patient with an acute illness with features resembling poliomyelitis, the diagnosis may be accepted as accurate, and is considerably strengthened if serological tests suggest an infection with poliomyelitis virus

There is no question of the supreme value of tissue-culture methods in the isolation of virus and in the performance of virus-neutralization tests Such methods have the following main advantages over the inoculation of monkeys Tissue cultures are very much less expensive than monkeys, and considerable numbers can be readily prepared The effect of poliomyelitis virus on tissue cultures may be evident within as short a time as 2-7 days following inoculation, and is visible without the necessity for staining Finally, tissue-culture techniques lend themselves to use in titration methods, and titres of virus and of antibody can be accurately determined by these means

The simplest technique is probably to use a roller-tube system consisting of human embryonic tissue or of monkey testis or kidney with a nutrient containing horse serum and embryo extracts In laboratories accustomed to the preparation of synthetic media, Mixture No 199 will be found a useful alternative to media containing animal sera or embryo extracts

It would clearly be of little advantage to use tissue cultures unless they are as sensitive as monkeys to the presence of poliomyelitis virus In a small series of cases studied in 1952 by the inoculation of stools in monkeys and in monkey testicular tissue, we concluded that the monkey-inoculation technique was more sensitive[17] However, this finding was not confirmed in a much more extensive experience in 1953, when we tested 100 specimens of stool from paralytic cases These specimens were collected and shipped under a wide variety of conditions, mostly during the heat of summer, yet, by means of the technique already described, in accordance with which initial seedings were made in flask cultures of monkey kidney, no less than

91 cytopathogenic agents were recovered Some of these strains may prove not to be true poliomyelitis virus; nevertheless, the recovery-rate is very high This rate may be compared with that of 85% obtained by monkey inoculation in previous years (27 positive out of 32 specimens tested). Other workers have also reported a satisfactory recovery-rate of poliomyelitis virus by the inoculation of tissue cultures.[40, 42, 61] It is thus probable that the two techniques are of comparable sensitivity.

It is well recognized that Coxsackie viruses are frequently encountered in the stools of cases of paralytic as well as of non-paralytic poliomyelitis, and it is natural to inquire whether these viruses may give rise to errors in interpretation It would appear that many strains of Coxsackie virus fail to grow in tissue cultures, and thus do not confuse the picture. Some strains grow in flask cultures but, in our experience, these have not produced cytopathogenic changes in roller-tube cultures [17]

A more serious difficulty is occasioned by the presence in stools of agents which cause a cytopathogenic effect indistinguishable from that caused by poliomyelitis virus [17, 40, 49, 56] These agents are not neutralized by antisera to the three known types, and are found more commonly in the stools of non-paralytics than paralytics. We have isolated 10 such agents in Toronto 3 from paralytic patients and 7 from non-paralytics

The role of serological examinations in the laboratory diagnosis of poliomyelitis remains to be discussed Both virus-neutralizing and complement-fixing antibody develop in the course of poliomyelitis, the former antibody has been studied more intensively than the latter Both antibodies develop early in the illness and this places a serious limitation on the diagnostic value of serological tests Because of the widespread prevalence of subclinical infections, the serum of most adults contains antibody to at least one of the three types These features limit the possibility of demonstrating an increase in antibody level between acute- and convalescent-phase sera

In the most common application of the virus-neutralization test, the strain of virus isolated from the patient is tested with acute- and convalescent-phase serum The demonstration of a significant increase in antibody suggests that the virus isolated was in fact responsible for the illness in question Such tests are now carried out in tissue cultures Because of the prevalence of the untypeable agents previously mentioned, strains to be tested with homologous serum must also be typed. It is not yet possible to say whether neutralizing titres are higher in the sera of recent convalescents than in the sera of members of the general population.

Virus-neutralization tests may also be used when the only specimens available for diagnosis are samples of blood from patients suffering from both the acute and convalescent phases of poliomyelitis. In such instances,

the sera should be tested against representative strains of each type. The presence of a significant increase in titre to one of the 3 types would suggest that a strain of that type had caused the illness

Virus laboratories are not infrequently asked to examine for neutralizing antibody a single sample of serum taken in convalescence. Very little significance can be attached to the results of such an examination, but if such a specimen fails to contain antibody to any of the three types, one may justifiably conclude that the recent illness was not poliomyelitis.

Although observations with the complement-fixation test are as yet limited, it would appear that the presence of positive complement-fixation is indicative of a comparatively recent infection. It has not been shown conclusively that complement-fixing antibody develops before the neutralizing antibody, as occurs in some other infections. Any such demonstration might establish the complement-fixation test as a valuable aid to early diagnosis, but of course it would then be more than ever necessary to obtain a sample of blood as soon as possible

Annex 1

ISOLATION AND IDENTIFICATION OF POLIOMYELITIS VIRUS IN THE LABORATORY *

A. Precautions

Isolation of poliomyelitis virus from human and other sources usually requires a team of two or more workers and their work is not without danger, since the percentage of laboratory workers who have accidentally acquired poliomyelitis in the laboratory is appreciable For obvious reasons, therefore, sterile precautions must be taken in handling infective materials Gowns should be worn at all times, and for certain procedures gloves, cellophane masks, and eye-shields are necessary as well Persistent vigilance is required on the part of the director of the team engaged in this work to ensure that the individual members consistently take the necessary precautions

B. Sources of Material

Poliomyelitis virus can be isolated by monkey inoculation and by tissue-culture inoculation, from a number of materials derived from man, and from extra-human sources such as sewage and flies However, even using the most careful technique, negative results are a common experience If human material is being tested, the chances of successful isolation are greater if the material is obtained early in the disease, within the first 7-8 days, dating the onset of the disease from the first onset of fever—even though the symptoms be slight—(i e , the " minor illness " if such occurs) and not from the

* Excerpt from the first report of the WHO Expert Committee on Poliomyelitis (*Wld Hlth Org techn Rep Ser* 1954, 81 47)

onset of paralytic symptoms, which may actually occur late in the acute infection Sometimes when it is important to obtain a strain of poliomyelitis virus quickly from a given outbreak, it is useful to visit the homes of hospitalized patients, and to determine whether any other members of the family are ill with symptoms suggesting an earlier stage of the disease If so, they may furnish more-valuable specimens than does the patient in the hospital

1 *Human autopsy material* from which the virus has been frequently isolated includes.

(*a*) pons, spinal cord, and medulla, provided death has occurred 7-10 days from the onset, and

(*b*) intestinal contents and intestinal wall

In removing central-nervous-system tissue at autopsy, an assistant should be ready with sterile gloves and several sets of sterile instruments, or at least with the means for reboiling the same instruments frequently ** Favoured sites from which virus may be isolated are the medulla, and the cervical and lumbar sections of the spinal cord, pieces about 2 cc in size should be taken from these areas and placed in a sterile Petri dish The cauda equina is not recommended as a source of virus At the same time, other appropriate sections of the cord should be placed in fixing solution for subsequent histological examination

2 *Clinical cases and carriers as a source of material*

Poliomyelitis virus has been isolated frequently from

(*a*) faeces,

(*b*) rectal swabs (some faecal material should be obtained on the swab, if possible),

(*c*) pharyngeal washings (15-30 ml),

(*d*) throat swabs (2 from each patient)

A reliable source of virus is human faecal material, since poliomyelitis virus is found for a longer time in the intestinal tract than elsewhere within the body, and has been isolated from faeces during the incubation period, during the acute disease, and in convalescence Nevertheless, the optimal time for collecting specimens in all cases, paralytic, non-paralytic, and abortive, is early in the course of the infection Virus may also be recovered from asymptomatic carriers who are often present in association with known cases of poliomyelitis

The virus is not found in spinal fluid, but recently it has been detected in the blood during the incubation period and during the minor illness However, blood is not a favoured source of virus for isolation

C. Collection of Material from Patients and Carriers

1 *Faeces*

A 15-25 g specimen is desirable Small wide-mouthed jars are useful as containers The specimen should *preferably be kept frozen, or at least kept cold, until tested*

2 *Rectal swabs*

If a stool specimen cannot be obtained, a rectal swab is often a useful substitute A moist sterile swab is inserted well into the rectum and manipulated until faecal material

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** *The main reason for maintaining a sterile technique is that the chances of bacterial contamination are minimized, which is important when central-nervous-system tissue is to be used for intracerebral monkey inoculation or for tissue-culture inoculation*

is found to be adhering to it The swab is then placed in a test-tube containing 1 ml of sterile water or broth It is important that the specimen be tested promptly or else kept frozen

3 *Pharyngeal washings*

Various types of irrigating fluid, such as sterile distilled water or broth, may be used to obtain pharyngeal washings from patients or suspected carriers of the virus The irrigating fluid is introduced into the patient's mouth, either from a drinking glass or through a large glass syringe without a needle attached to it The patient is then encouraged to gargle the material which is collected in a glass or a small sterile basin. The procedure is carried on over a period of at least three minutes, using the same fluid repeatedly Not more than 30 ml of irrigating fluid should be used

4 *Throat swabs*

Material is obtained by rubbing the oropharynx vigorously with two sterile cotton swabs, which are immediately transferred to a test-tube containing 1-2 ml of sterile water or broth The specimens should be tested promptly or kept frozen

D. Storage of Material

Material awaiting testing or shipment may be held for short periods at refrigerator temperature (0°-4°C) For longer storage it should preferably be frozen, or it may be kept in 50% glycerol

Freezing

Ordinary glass test-tubes containing more than 1 ml of fluid are liable to crack when frozen , therefore, if fluid material is to be frozen it should be placed in special containers, i e , either nitro-cellulose tubes or thick-walled glass containers Freezing may be accomplished by placing the tubes in the freezing compartment of an electrically driven refrigerator, or in a specially constructed insulated box containing solid carbon dioxide (dry ice) which may maintain a temperature of from -20° to -70°C For the preservation of poliomyelitis virus, unlike certain other viruses, temperatures below -20°C are not essential

Glycerol

Only the purest brands of glycerol should be used for the preservation of poliomyelitis virus The glycerol should be mixed with an equal volume of physiological saline before use

Some points with regard to the use of glycerol are

(1) do not put more than 4 or 5 small pieces of tissue in 50 ml of glycerol-saline, and

(2) do not allow the tissue to remain untested any longer than is necessary However, as 50% [illegible]

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(1) do not put more than 4 or 5 small pieces of tissue in 50 ml of glycerol-saline, and

(2) do not allow the tissue to remain untested any longer than is necessary However, as 50% glycerol has a slow bactericidal action, it may be useful to allow bacteriologically contaminated specimens to remain in it for a few days before testing them for virus Although poliomyelitis virus has been known to survive in 50% glycerol for many years, it has also died out in this medium after a few months or even weeks

Lyophilization

As a method of preserving poliomyelitis virus, lyophilization has been accomplished with various diluents such as 10% monkey serum, and mucin. However, results are irregular and lyophilization is not recommended for this purpose

E. Shipping of Specimens

If frozen material is to be shipped short distances, it should be sent in a proper container, such as an insulated box containing dry ice, or a well-packed thermos flask containing dry ice Special care in packing thermos bottles is essential or breakage may easily occur

The necessity of keeping all specimens cool probably varies with the circumstances †

A more practical method for shipping involves the use of 50% glycerol Autopsy specimens, stool specimens (small in amount), and the sediment from rectal swabs, pharyngeal washings, and throat swabs may all be sent at room temperature in 50% glycerol. For this purpose it is convenient to use small wide-mouthed bottles with tightly stoppered or capped orifices, and, for safety, the top of each bottle should be wrapped with several layers of water-proof tape Before preparing such material for inoculation the fragments of tissue or particulate matter should be washed several times in saline solution to remove some of the glycerol

F Monkey Inoculation

The following species of monkeys have been most often used in poliomyelitis work

Macaca mulatta the rhesus monkey, usually from India

Macaca cynomolgus and/or *irus* or *mordax* the cynomolgus (or Java) monkey from the East Indies, Philippine Islands, or Malaya

Cercopithecus aethiops sabaeus and *griseoviridis* the green African and grivet monkeys from West and East Africa

Cercopithecus aethiops centralis the vervet monkey from West, Central, and South Africa

Cebus capucina the ringtail or capuchin monkey from South America

Of this series the rhesus monkey has been most widely used

One, two, or three monkeys may be used for testing each specimen It is considered conservative practice to use one animal

The choice of the route of inoculation is based on the following principles The intracerebral route is the most delicate, but if the inoculum contains an excess of bacteria, the inoculated monkey may succumb with a brain abscess before it acquires experimental poliomyelitis The intranasal route is quite reliable and not dangerous to the animal, but is cumbersome and time-consuming The intra-abdominal route is less reliable, but is simple and safe and is often used as an adjunct to the other two

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† The survival time of poliomyelitis virus in human stools at room temperature is variable, but the virus remains viable in this medium for several weeks at refrigerator temperature.

1 *Preparation of inocula from nervous tissue*

Weighed fragments of medulla or spinal cord (1 0-1 5 g are usually sufficient) are ground in a sterile mortar containing sterile sand or an abrasive, with enough sterile water, not more than 1 or 2 ml at first, to produce a fairly thick paste Grinding is usually continued for at least five minutes Sufficient cold, sterile, distilled water is then added to make a 10% suspension, and antibiotics are added to yield a final concentration of 500 units of penicillin and 500 micrograms of streptomycin per ml The suspension is then transferred to a cold centrifuge tube where it is spun at low speed (2,000 revolutions per minute (r p m)) for five minutes The supernatant fluid will be opalescent, but should contain no particles large enough to plug the lumen of a small needle. It is advisable to prepare from 10 ml to 15 ml of suspension so that some of the material may be kept frozen for possible future use

1 1 *Intracerebral inoculation*

The monkey to be inoculated should be properly marked beforehand (by tattooing if feasible) It is anaesthetized, commonly with ether, the hair is clipped away from the forehead and top of the head, and the area is then shaved The site of inoculation is the central area over the frontal lobe on the right or left side The skin over the area is rubbed well with iodine and alcohol Trephining of the skull can be accomplished by using a sharp instrument (half of a pair of scissors is satisfactory) which will bore a hole 1-2 mm in diameter, through which 1 ml of the suspension to be tested can be injected intracerebrally It is common practice to inject 1 ml or less, to a depth of about 1 cm Some workers advise dividing the inoculum into two parts of 0 5 ml each; each part is then inoculated deep into the hypothalamus, 0 5 ml on the left and 0 5 ml on the right

If it is particularly important to demonstrate virus, the animal may be re-inoculated intracerebrally with the same material at intervals of one, two, or three weeks Furthermore, the same monkey can be inoculated by other routes (1) intranasally, 2 ml of the original suspension should be instilled into the etherized animal's nares, and the process repeated on the subsequent days (see below), and (2) intra-abdominally, 5-15 ml can also be given intra-abdominally

1 2 *Intranasal inoculation*

In carrying out intranasal instillation, it is useful but not essential to anaesthetize the monkey lightly with ether 2 ml of the inoculum are allowed to drop directly into each nostril either from a pipette or from a syringe fitted with a blunt needle During this process an assistant should hold the monkey underneath a fixed glass plate in order to limit splattering of the infectious material Both operators should wear gowns and gloves, and if no glass plate is available they should wear goggles and cellophane masks Instillation of material should preferably be repeated daily over a period of six days.

2 *Preparation of inoculum from faecal material*

Relatively large (25-50 g) specimens are sometimes desirable (but not essential). In preparing the material for monkey inoculation, various procedures may be used; none of them is easy, and a laboratory which is beginning to work in this field may expect to encounter difficulties which can be overcome through a process of trial and error.

It may be desirable to divide the original specimen of faeces (or fluid from the rectal swab) into two equal portions, one being kept frozen or in the refrigerator for future

use should the test be unsatisfactory, or should there be other reasons to retest the specimen

The intracerebral route of inoculation of faecal material (alone or in combination with other routes) has been more successful in some hands than in others. The chief difficulty is the readiness with which some faecal suspensions give rise to brain abscesses in the inoculated monkeys.

A satisfactory method is to prepare a 10% suspension from the stool specimen in cold, sterile, distilled water in a tightly-stoppered 250-ml flask containing glass beads, after frequent shaking, the specimen is allowed to settle in the cold The supernatant fluid is then poured off into another flask, and it is again well shaken and allowed to settle From the supernate of the second flask, the material is divided into two parts, I and II, generally amounting to between 20 and 25 ml each

Part I (20 ml), without further treatment, is kept at refrigerator temperature for intranasal use (see above)

Part II (25 ml) is immediately centrifuged at relatively low speed (15 minutes, 2,000 r.p.m.), and to the supernate, 15% ether is added as a bactericidal agent †† together with penicillin and streptomycin solution to make a final dilution of 500 units and 500 micrograms per ml, respectively The etherized suspension is kept in a stoppered container in the refrigerator

A sample of Part II (5-10 ml) is placed in a small centrifuge tube within the centrifuge cup in the refrigerator to chill the specimen In order to remove bacteria, it is again centrifuged at 4,500 r p m , or at higher speeds if such are available, for half an hour to one hour 3 ml are removed from the supernate and 0 1 ml of this is cultured on a blood-agar plate. This specimen, Part III, is set aside in the refrigerator for *intracerebral inoculation*

If, after 24 hours, the growth of bacteria is minimal or absent, the fluid from Part III below the layer of ether is removed, and an amount not exceeding 1 ml is inoculated intracerebrally

The same monkey may be inoculated intra-abdominally with the residuum of Part II, using an inoculum of not more than 10-12 ml The concentration of ether (15%) and antibiotics used in Part II usually, but not always, destroys or diminishes the number of bacteria in the suspension sufficiently to permit of intra-abdominal injection of 10-12 ml without fear of inducing fatal peritonitis

If only the washings from a rectal swab are available, the volume of material will be small, but may be diluted to a volume of 3-5 ml, 15% ether and antibiotics as above are added, and the suspension is treated as are Parts II and III and used for intracerebral inoculation

3. *Pharyngeal washings and throat swabs*

The washings are transferred to a sterile flask containing glass beads, the flask is tightly stoppered and shaken for 10 minutes The suspension is subjected to light centrifugation (2,000 r p.m for 10 minutes), 10% ether and antibiotics are added, and it is allowed to stand in the refrigerator overnight On the following day, the etherized material is inoculated intracerebrally in 1-ml amounts Intracerebral inoculation may be supplemented by intra-abdominal injection of 10 ml of the etherized suspension

Other methods More-delicate methods of handling these suspensions exist, which include in particular the use of the ultracentrifuge in preparing material for intracerebral

†† If the material is to be inoculated into tissue culture ether need not be added

inoculation. This instrument is a valuable but not an essential part of the usual poliomyelitis laboratory's equipment

4 *Observation of inoculated monkeys*

Monkeys inoculated with material suspected of containing poliomyelitis virus should be observed for at least four weeks It is good practice to examine and exercise these animals daily during this period By this method early signs of experimental poliomyelitis, such as tremor, ataxia, and weakness of the limbs, can be detected, and the animal can promptly be sacrificed at an appropriate time if a strain of virus is desired for passage or storage A further reason for daily examinations is that, soon after an intracerebral inoculation, the animal may develop a spastic paralysis, often taking the form of hemiplegia, resulting from an upper motor neuron lesion caused by local trauma or necrosis of the brain It is important not to confuse this with the flaccid paralysis resulting from poliomyelitis

Temperature readings should be taken daily, preferably at the same time each day, using individual rectal thermometers which are sterilized in a strong disinfectant solution between use The usual rectal temperature of rhesus monkeys varies from 102.2°F (39°C) to 103 5°F (39 7°C), but temperatures up to 104°F (40°C) are not particularly abnormal The onset of the experimental disease (induced with human strains of virus), may follow an incubation period of from 4 to 25 days. This is usually, but by no means always, heralded by a rise of temperature to between 104°F (40°C) and 106°F (41 1°C) Fever is maintained from one to six days, during which time other signs may appear quickly or slowly These consist of ruffled fur, nervousness, tremors (often first noticeable as a fine tremor of the ears), ataxia, and finally weakness, to be followed by definite paralysis most easily detectable in the extremities, although it may involve the face, neck or back With the development of considerable paralysis there is usually an abrupt fall in temperature. Even in the absence of signs of infection it may be wise to sacrifice the animal as a routine at the end of the 30-day period of observation It is not good practice to use the same animal again for poliomyelitis investigation

4 1 *Autopsy of monkeys*

An animal can be sacrificed by the injection of ether into the heart. Before incising the skin, the fur of the back and head of the animal should be swabbed with lysol solution The brain and cord are removed first, using two or three changes of sterile instruments It is best to remove the cord with the dura intact, and then to open the dura with sterile scissors and forceps Several sections are taken from the cervical, dorsal, and lumbar regions of the cord, and from the medulla One of each is placed in fixing solution for histological examination, and several of each are kept for passage or storage either frozen or in 50% glycerol

4 2 *Criteria for a positive result*

The most important evidence of the experimental disease in the monkey is found on histological examination of sections taken from the spinal cord The lesions should be unequivocal before a positive diagnosis of the isolation of poliomyelitis virus is accepted Such lesions are generally manifest in the grey matter of the spinal cord involving in particular the ganglion cells in the anterior horns The lesions pass through several stages, but when fully developed they are characterized by destruction of neurons and neuronophagia, and, prominently by perivascular and interstitial round-cell infiltration In the brain, lesions are not likely to be extensive and may be scattered, often in the base of the brain and not uncommonly in the motor cortex The cerebral

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lesions are not regarded as convincing evidence of poliomyelitis unless other lesions are also found in the medulla and spinal cord. By adopting this standard, experimental poliomyelitis is less likely to be confused with other types of encephalomyelitis, or with the areas of inflammation surrounding a brain abscess or brain injury. In many instances it may be wise to pass the strain in tissue culture and to identify it by neutralization tests using the three types of poliomyelitis antisera; or to pass the strain of virus to another monkey for confirmatory evidence Under certain circumstances, it may also be wise to inoculate the strain intracerebrally in adult and suckling mice, rabbits, and guinea-pigs If these animals develop encephalomyelitis it is probable that either the virus is not poliomyelitis virus, or if mice alone are infected, it may be a type 2 (Lansing) strain of poliomyelitis virus which can infect rodents These possibilities can be checked by further tests, preferably including attempts to type the virus

A negative result should be recorded if the animal fails to show typical lesions in the spinal cord In general, the failure of the inoculated animal to show the appropriate signs of infection during the period of observation is a fair indication of a negative result, but non-paralytic or apparently silent infections may occur in a small percentage of inoculated monkeys

An incomplete or unsatisfactory result is recorded if the inoculated monkey dies from some cause other than poliomyelitis before the 30-day period of observation is complete

Annex 2

PREPARATION OF STOOLS BY ULTRACENTRIFUGATION

1 Approximately 5 g of stool are placed in a weighed glass shaking-bottle with glass beads

2 The weight of the specimen is determined, and a 10% suspension is prepared in normal saline

3 The bottle is stoppered, and shaken until the stool is evenly dispersed

4 The suspension is filtered through sterile gauze into 50-ml centrifuge tubes

5 The filtrate is centrifuged at 3,000 r p m for 20 minutes

6 The supernatant is distributed to Lusteroid tubes and centrifuged at 40,000 r p m in a Spinco centrifuge for 1 hour at 4°C

7 The supernatant is discarded and the deposit resuspended in 2 ml normal saline containing 500 units of penicillin and 250 μg of streptomycin per ml

8 The resuspended extract is centrifuged at 1,500 r p m for 5 minutes. The deposit is discarded

9 The supernatant is stored frozen

Annex 3

PREPARATION OF SUPPLIES FOR TISSUE CULTURE

Water

It is very important that water-supplies used in the final rinsing process of cleansed glass-ware, and particularly in the preparation of synthetic medium, be as free as possible from heavy metals Water can be rendered practically free of heavy metals by distillation

followed by glass redistillation, passage of distilled water through a mixed-bed ion-exchange column is a very convenient means of replacing glass redistillation * Water prepared by ion-exchanging may however be pyrogenic. Under circumstances where a pyrogen-free water is required, glass redistillation is recommended

Solutions used in cleansing of glass-ware

1 1% hydrochloric acid.

2 As a detergent, Alconox ** solution is prepared in the proportion of 1½ tablespoons to 1 gallon (3 8 litres) of warm tap water

3. To prepare concentrated acid cleansing solution, 0.5% sodium chlorate and 0 5% sodium nitrate are added to concentrated Analar-grade sulphuric acid The resultant dark brown mixture is heated to 90°C in a Pyrex container placed in a bucket of sand On cooling, the liquid becomes nearly colourless

Cleansing of new unused glass-ware

The glass-ware is placed in 1% HCl for several hours to remove excess alkali and is then treated as used glass-ware

Cleansing of used glass-ware that can be boiled

1 The glass-ware, following sterilization in the autoclave, is rinsed under hot tap water to remove loose material.

2 It is then boiled in detergent solution for 15 minutes.

3 Next, the glass-ware is rinsed under warm tap water with brushing

4 It is then submerged overnight in cold concentrated acid cleansing solution

5 The acid is removed by rinsing the glass-ware ten times in running hot tap water.

6 The glass-ware is then submerged in once-distilled water for two hours

7 Next, the glass-ware is submerged in glass-redistilled (or ion-exchanged) water for two hours or overnight

8 Finally, the glass-ware is dried in a hot-air oven

Cleansing of used glass-ware that cannot be boiled

1 Such glass-ware is cleansed as directed above, with the exception of steps 1 and 2, which are omitted

2. It is then rinsed in 95% glass-distilled alcohol before drying

New, unused, black rubber stoppers

1 Stoppers of this type are boiled in N/2 NaOH for 3 minutes

2 Next, they are rinsed in tap water

3 They are then boiled in N/2 HCl for 3 minutes

4 Next, the stoppers are rinsed in tap water.

5 Finally, they are rinsed in ion-exchanged water

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* Healy, G M, Morgan, J F & Parker, R C (1952) *J biol Chem* 198, 305

** Obtainable from Canadian Laboratory Supplies, 3701 Dundas St W., Toronto, Ontario, Canada

New, unused, white rubber and used black rubber stoppers

1 Stoppers of this type are boiled in distilled water for 3 minutes

2 The final rinsing is in ion-exchanged water.

New rubber tubing

1 New rubber tubing is boiled in N/2 NaOH for 3 minutes

2 Next, it is rinsed in tap water.

3 The tubing is then boiled in N/2 HCl for 3 minutes; the acid is forced through the tubing with a syringe

4 Next, the tubing is washed with warm tap water, and flushed with tap water for 30 minutes

5 Finally, at least a litre of ion-exchanged water is run through the tubing

Used rubber tubing

Used rubber tubing is treated as directed in steps 4 and 5 above.

Instruments

1 The instruments are washed with soap and warm water

2 They are then rinsed thoroughly with running tap water

3 Next, they are placed in 95% alcohol

4 Finally, the instruments are dried in an open drying oven

Annex 4

PREPARATION OF SYNTHETIC MEDIUM NO. 199

GEORGE M HEALY, B A
RAYMOND C PARKER, Ph D.

Connaught Medical Research Laboratories, University of Toronto, Ontario, Canada

Stock Solutions

The components of synthetic medium No 199 (table I) are obtained commercially and are employed without further purification In this description, the stock solutions are designated by Arabic numerals followed by letters, in parentheses, to indicate their relationship to the lettered stock solutions listed in the original publication *

[illegible] through a Barnstead still [illegible] alternative, distilled water

* Morgan, J. F., Morton, H J & Parker, R C (1950) *Proc Soc. exp Biol (N Y)* 73, 1

** Healy, G M, Morgan, J F. & Parker, R C (1952) *J biol Chem.* 198 305

All stock solutions except Nos 1 and 2 are stored at 4°C, without filtration, for periods not exceeding 30 days A fresh lot of solution 1 is made up each time a new *batch of medium* is prepared If it is desired to store soln. 1, it should be filtered and stored in 500-ml quantities in the refrigerator. Soln. 2, which tends to form a precipitate at 4°C, is stored at room temperature.

The solutions are prepared as follows

Soln 1 (A): To 400–450 ml of water, stirred continuously, and heated to about 80°C, are added the following phenol red (water-soluble), 20 mg; *l*-arginine monohydrochloride, 70 mg; *l* histidine monohydrochloride, 20 mg, *l* lysine monohydrochloride, 70 mg, *dl*-tryptophane, 20 mg; *dl*-phenylalanine, 50 mg, *dl*-methionine, 30 mg, *dl*-serine, 50 mg, *dl*-threonine, 60 mg, *dl*-leucine, 120 mg; *dl*-isoleucine, 40 mg, *dl*-valine, 50 mg, *dl*-glutamic acid monohydrate, 150 mg, *dl*-aspartic acid, 60 mg; *dl*-alanine, 50 mg; *l*-proline, 40 mg, *l*-hydroxyproline, 10 mg, glycine, 50 mg; and sodium acetate, 50 mg The solution is cooled to room temperature and 100 mg of *l*-glutamine are added The ingredients of Earle's balanced salt solution are then added, as follows · sodium chloride, 6 8 g, potassium chloride, 0 4 g, calcium chloride, 0.2 g, magnesium sulfate ($MgSO_4 \cdot 7H_2O$), 0 2 g, sodium dihydrogen phosphate ($NaH_2PO_4 \cdot H_2O$), 0 14 g; sodium bicarbonate ($NaHCO_3$), 2.2 g; and *glucose*, 1 0 g *Finally*, 500 mg of dihydrostreptomycin sulfate are added, and the solution is made up to 500 ml with water.

Soln 2 (B) · 200 mg of *l*-tyrosine and 100 mg of *l*-cystine are dissolved *with moderate* heating in 100 ml of 0 075 N HCl

Soln 3 (C) The following B vitamins are dissolved in 200 ml (final volume) of water niacin, 25 mg, niacinamide, 25 mg, pyridoxine hydrochloride, 25 mg; *pyridoxal hydrochloride*, 25 mg; thiamine hydrochloride, 10 mg, riboflavine, 10 mg, calcium pantothenate, 10 mg, *i*-inositol, 50 mg, *p*-aminobenzoic acid, 50 mg, and choline chloride, 500 mg The stock solution consists of a 1/50 dilution of this solution with water

Soln 4 (D) The following are dissolved in 100 ml (final volume) of water ascorbic acid, 50 mg; glutathione, 50 mg, and cysteine hydrochloride, 100 mg The stock solution consists of a 1/100 dilution of this solution with water.

Soln 5 (E) 10 mg of *d*-biotin are dissolved in approximately 50 ml of water containing 1 ml of N HCl (to increase stability on storage), and the final volume is *adjusted to 100 ml* The stock solution consists of a 1/100 dilution of this solution with water

Soln 6 (F) 10 mg of folic acid (insoluble in pure water) are dissolved in 100 ml of Earle's balanced *salt solution*, i e, the substances and amounts as listed for soln 1, but dissolved in 1 litre of water

Soln 7 (G, H, J, K) Two alcoholic tinctures are required to prepare this combined stock solution cholesterol 10 *mg per ml in* 95% *ethanol*, and menadione (vitamin K) 10 mg per ml in 95% ethanol The following lipid-soluble vitamins are added to a 100-ml volumetric flask *calciferol* (vitamin D), 10 mg, dissolved in 1-ml of the tincture of cholesterol, vitamin A, 10 mg, dissolved in another 1-ml portion of the tincture of cholesterol, and tincture of *menadione* (*vitamin* K), 0 1 ml Finally, 10 ml of a 5% aqueous solution of Tween 80 are added *to* *the flask* The mixture is then made up to a final volume of 100 ml and warmed to dissolve the cholesterol The stock solution consists of a 1/10 dilution of this *solution with water*.

Soln 8 (I) 10 mg of disodium-α-tocopherol phosphate (vitamin E) are dissolved in water to make a *final volume of 100 ml* The stock solution consists of a 1/100 dilution of this solution with water

Soln 9 (L). 89 7 mg of adenine hydrochloride hemihydrate are dissolved in a *final* volume of 100 *ml of water*.

Soln 10 (M). The following purines and pyrimidines are dissolved in 200 ml (final volume) of water made alkaline with 2 drops of concentrated ammonium hydroxide: guanine hydrochloride, 10 mg, hypoxanthine, 10 mg; thymine, 10 mg; uracil, 10 mg; and monosodium xanthine, 11 4 mg

Soln 11 (N) 100 mg of *d*-ribose and 100 mg of *d*-2-desoxyribose are dissolved in 100 ml (final volume) of water

Soln 12 (O). 10 mg of 5-adenylic acid are dissolved in 100 ml (final volume) of water

Soln 13 (P) 260 mg of sodium adenosine triphosphate are dissolved in 50 ml (final volume) of water The stock solution consists of a 1/10 dilution of this solution with water

Soln 14 (Q): 36 mg of ferric nitrate $Fe(NO_3)_3 \cdot 9H_2O$ are dissolved in 100 ml (final volume) of water. One drop of concentrated nitric acid is added to prevent hydrolysis during storage.

Preparation of One Litre of Medium No. 199

The various constituents of the final medium (as also the ingredients of solution 1) are mixed in a distillation flask with a large central neck and a smaller, vertical, side neck The large central neck accommodates a bent glass stirring-rod attached to a small motor, and the ingredients are added through the side neck The stock solutions are combined as follows

		Solutions	*ml*
1	(A)	Amino acids, acetate, glutamine, Earle's solution	500 0
2	(B)	Tyrosine, cystine	20 0
3	(C)	B vitamins	10 0
4	(D)	Vitamin C, cysteine, glutathione	10 0
5	(E)	Biotin	10 0
6	(F)	Folic acid	10 0
7	(G, H, J, K)	Vitamins A, D, and K, cholesterol, Tween 80	10 0
8	(I)	Vitamin E	10 0
9	(L)	Adenine hydrochloride	10 0
10	(M)	Purines, pyrimidines	6 0
11	(N)	Ribose, desoxyribose	0 5
12	(O)	5-Adenylic acid	2 0
13	(P)	Adenosine triphosphate	2 0
14	(Q)	Ferric nitrate	2 0

The final volume is adjusted to 1 litre by the addition of water, and the completed medium is sterilized by filtration (Corning UF fritted glass) and stored in the dark at room temperature Just before use, 500 units per ml (final) of potassium penicillin G are added.

Preparation of Larger Volumes of Medium No. 199

... volume of ... of Medium

TABLE 1 COMPONENTS OF SYNTHETIC MEDIUM No. 199 (MG PER 1,000 ML)

Component	mg per 1,000 ml
Inorganic salts	
NaC	6,800 0
KCl	400 0
$CaCl_2$	200 0
$MgSO_4$, $7H_2O$	200 0
NaH_2PO_4 H_2O	140 0
$NaHCO_3$	2,200 0
Fe — as $Fe(NO_3)_3$	0 1
Amino acids	
l-Arginine	70 0
l-Histidine	20 0
l-Lysine	70 0
l-Tyrosine	40 0
dl-Tryptophane	20 0
dl-Phenylalanine	50.0
l-Cystine	20 0
dl-Methionine	30 0
dl-Serine	50 0
dl-Threonine	60 0
dl-Leucine	120 0
dl-Isoleucine	40 0
dl-Valine	50 0
dl-Glutamic acid	150 0
dl-Aspartic acid	60 0
dl-Alanine	50 0
l-Proline	40 0
l-Hydroxyproline	10 0
Glycine	50 0
l-Cysteine hydrochloride	0 1
Vitamins	
Thiamine	0 01
Riboflavine	0 01
Pyridoxine	0 025
Pyridoxal	0 025
Niacin	0 025
Niacinamide	0 025
Pantothenate	0 01
Biotin	0 01
Vitamins (continued)	
Folic acid	0 01
Choline	0 50
Inositol	0.05
p-Aminobenzoic acid	0.05
Vitamin A	0 10
Ascorbic acid (vitamin C)	0 05
Calciferol (vitamin D)	0 10
α-Tocopherol phosphate (vitamin E)	0 01
Menadione (vitamin K)	0 01
Lipid sources	
Tween 80 * (oleic acid)	5 0
Cholesterol	0.2
Nucleic acid derivatives	
Adenine	10 0
Guanine	0.3
Xanthine	0 3
Hypoxanthine	0.3
Thymine	0.3
Uracil	0.3
Adenosine triphosphate	10 0
Adenylic acid	0 2
Ribose	0.5
Desoxyribose	0 5
Miscellaneous	
Sodium acetate	50 0
Glutathione	0 05
l-Glutamine	100 0
Glucose	1,000 0
Phenol red (pH indicator)	20 0
Ethanol (as initial solvent for vitamins A, D, & K, and cholesterol)	16 0

* Aqueous Tween 80 also serves as the final diluent of an alcoholic stock solution of vitamins A, D, & K, and cholesterol.

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THE PRESENT STATUS OF TISSUE-CULTURE TECHNIQUES IN THE STUDY OF THE POLIOMYELITIS VIRUSES

JOHN F. ENDERS, Ph D

Chief, Research Division of Infectious Diseases, Children's Medical Center, Boston, Mass., USA

Associate Professor of Bacteriology and Immunology, Harvard Medical School, Boston, Mass., USA

Following the demonstration in 1949 and 1950 that the poliomyelitis viruses could be cultivated in vitro in extraneural tissues of human [8, 49, 57] and simian origin [49, 53] and the observation [36] that these agents destroyed the cells in which their multiplication occurred, tissue-culture methods have been applied on an ever-widening scale to the investigation of various aspects of poliomyelitis. The principal reason for this increasing application of the method consists in the fact that for many purposes the tissue culture affords a satisfactory substitute for the experimental animal. Tissue cultures can be had in practically unlimited numbers, are relatively inexpensive to prepare and maintain, and have proved at least as sensitive in the detection of small quantities of virus as monkeys or mice. The destructive or cytopathogenic effect of the viruses on cultured cells can be regarded as analogous to the death or paralysis of the infected animal. This effect, which is readily observed and easily recognizable under low magnification, provides a satisfactory criterion not only for the presence of virus in a variety of materials such as faeces, nervous tissue, or throat washings, but also for determining the end-point in quantitative assays of viral activity. Tissue-culture techniques have also been adapted to the production of large quantities of virus for use as vaccines, to the analysis of the effect of the addition of drugs, metabolites, etc., on the growth of poliomyelitis viruses, and to the systematic study of other factors involved in their multiplication.

Since the cytopathogenic properties of the poliomyelitis viruses are inhibited in the presence of homotypic antibody, the tissue culture likewise has afforded a rapid and convenient means of titrating virus-neutralizing antibody, of determining the type of virus, and of defining the type and

Techniques Included in Group I

The following types of culture have been used for *maintaining or* propagating the tissues of man and monkey as *primary explants*

1. The so-called suspended-cell or suspended-fragment culture (Maitland)
2. The fixed-cell or fixed-fragment tube culture (roller or *stationary*)
3. The trypsinized fixed-cell culture of Dulbecco

Suspended-cell or suspended fragment culture

The suspended-cell or suspended-fragment culture was the type of culture in which evidence of the multiplication of poliomyelitis viruses in extraneural tissues was first obtained [8] Although it has usually been referred to as "the suspended-cell culture", it would seem more accurate to designate it "the suspended-fragment culture" Of all the types of tissue culture it is the easiest to prepare The procedure consists essentially in dividing the tissues into fragments (about 1 mm × 1 mm × 1 mm), usually by means of sharp scissors, and adding these to a flat-bottomed flask (Erlenmeyer) containing an appropriate medium The flask is stoppered tightly and kept at 35°-37°C At intervals, usually *of three* or four days, the medium is withdrawn as completely as possible and a fresh supply added Before addition of the viral inoculum, the medium is always changed at least once in order to remove antibody *specific for* the virus or other inhibitory factors that might be present in the original tissue Details of the preparation and maintenance of small suspended-cell cultures of human tissues for the cultivation of poliomyelitis virus have been described at length [55, 56]

A variety of tissues have been used in suspended-cell *cultures for* the growth of poliomyelitis virus These include . *various human* embryonic tissues, of which fragments of skin and skeletal *muscle, intestine*, and brain have been most extensively employed; [55, 56] *post-natal* human prepuce, [57] human [48] and monkey testis, [48, 53] *and human* [37] and monkey kidney [42] Of these, kidney tissue appears to be the most satisfactory since it yields a high *proportion* of good cultures and affords a high yield of virus [42] Media have consisted of either (1) a *mixture of* Hanks' balanced [illegible]

fluid phase was found between *the 8th and 12th* day of incubation Virus

measuring the amount of antibody developing after infection or the administration of viral antigens in the form of vaccines.

TISSUE-CULTURE TECHNIQUES USED FOR CULTIVATION OF POLIOMYELITIS VIRUSES

If tissue cultures are to become thoroughly useful tools in the hands of the virologist comparable to the lifeless media of the bacteriologist, they must be amenable to production in large and continuing quantity by techniques sufficiently simple and reliable to permit of the employment of relatively unskilled workers in certain phases of their manufacture Recognition of these requirements has led to numerous modifications in procedure, particularly by those who have in the last few years applied the method to the study of poliomyelitis Certain of these modifications have already contributed much to the ease and reliability with which large numbers of cultures may be prepared Without doubt future efforts will result in further advances along these lines

The modifications, however, in the traditional methods of tissue cultures [a] that have recently been introduced for the cultivation of poliomyelitis viruses render it impossible, at the present time, to describe a single procedure that has been universally, or even widely, employed by all workers in this field At the moment, therefore, I shall have to be content with summarizing certain techniques [b] that are currently in use in several different laboratories and with adding appropriate commentary in respect to the advantages and disadvantages of each.

For convenience of discussion, the procedures of tissue culture that have been employed for the cultivation of poliomyelitis viruses may be divided into two main groups The first (Group I) consists of those based on the use of primary explants of tissue fragments or cells, the second (Group II), of those depending upon the maintenance of cell stocks in continuous cultivation from which subcultures are prepared from time to time for experimental use The techniques of Group I have been applied to the cultivation of cells derived from man and the monkey, those of Group II have been applied so far only to the propagation of human cells.

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[a] For reviews of tissue-culture techniques as applied to the cultivation of viruses, see references 15, 18, 35, and 44

[b] It is not our purpose here to describe the various procedures in sufficient detail to permit the laboratory worker to undertake their actual performance For this purpose the original papers to which appropriate reference is made, should be consulted

of the virus can be recognized quickly and with much assurance of its specific nature. Assay of viral infectivity as well as of the antibody concentration of type-specific sera can thus be readily accomplished in roller-tube cultures of various sorts of human and simian tissues

In brief, roller-tube cultures are made [38] by distributing bits of minced tissue in a thin film of heparinized chicken plasma previously spread over a wall of a test-tube The plasma film is then clotted by the addition of a small quantity of chick embryonic extract A small amount of media (1 5 ml - 2 ml) is added and the tube is tightly stoppered The medium is changed at least once before virus is inoculated, and after that at various intervals or not at all depending upon the circumstances. If large amounts of actively metabolizing tissue are present, changes of medium are made at intervals of from two to four days, since a decline in the pH below 7 may cause extensive cell injury

A variety of media have been employed In our laboratory a mixture consisting of 10% bovine embryonic extract, 5% normal inactivated horse serum, and 85% to combine Hanks' balanced salt solution [16] and bovine serum ultrafiltrate in a proportion of 3 1, was used at first Lately, bovine amniotic fluid [7] has been substituted for the balanced salt solution and serum ultrafiltrate. Wood and his co-workers [58] and Youngner and his associates [60] have employed Mixture No 199 containing 2% normal horse serum, and Melnick & Riordan [25] have used an enzymatic hydrolyzate of lactalbumin together with bovine serum ultrafiltrate and Hanks' balanced salt solution. Recently Parker [33] has developed a modified form of Medium No 199, designated Medium No 703 This is said to provide conditions for long-continued survival and even for multiplication of cells

In the roller-tube culture, migration of the cells occurs readily about the implanted fragments, and with a complete type of medium—such as that containing embryonic extract, serum, and amniotic fluid—an active cell multiplication which may continue for weeks or even months takes place

With this system a variety of human tissues have been cultivated, including embryonic skin-muscle, lung, kidney, post-natal kidney, testis, prepuce, and myometrium [38] Among the tissues of the monkey, testis and kidney have been chiefly selected [22, 42, 60] Of all these tissues, human embryonic skin-muscle and lung, and post-natal human or simian kidney have proved to be the most satisfactory Embryonic cells, of course, are distinguished by more rapid migratory- and growth-rates, consequently they furnish cultures suitable for inoculation within 48-72 hours after the tissue is implanted The yield of virus in these tissues is relatively high and the cytopathic effect becomes rapidly apparent Of the post-natal tissues, kidney appears to be the most suitable since the cells migrate rapidly (from four to seven days), forming large sheets or plaques

production, however, begins before this time and may continue for several weeks

Growth of virus may be manifested indirectly in the tissue culture through its modifying influence on the production of acid by the tissue cells.[55, 56] This effect may be most conveniently observed by comparing at intervals the pH of cultures receiving inocula of material suspected to contain the virus with the pH of uninoculated control cultures As the virus attacks and destroys the cells, acid production is much diminished and may eventually cease

Recently the suspended-cell culture has been modified to meet the need for the production of large quantities of virus to be used in the preparation of vaccines. Farrell and his associates[10] have shown that representatives of all three antigenic types of poliomyelitis virus can be propagated in bottles containing 500 ml of medium (Mixture No. 199) and 5 g of minced kidney tissue. The cultures were made in Povitzky or diphtheria-toxin bottles which were placed on a rocking machine at 37°C. The highest titres were obtained between the 2nd and 7th days after inoculation of the Mahoney (I) and MEFI (II) strains of virus The total nitrogen content of the fluid containing the virus was low, not exceeding 0.29 mg per ml. This fact also is obviously of advantage in the case of materials to be used in the manufacture of vaccines

Comment As already indicated, the suspended-cell culture offers the advantage of simplicity as compared with other methods available for the propagation of poliomyelitis viruses. It would thus seem to be the technique of choice for the routine production of large quantities of virus For other purposes, however, such as the isolation and typing of viruses and the assay of infectivity or viral antibody, it is far less satisfactory than the procedures mentioned in the following paragraphs because of the longer period required before the results are available and the relative inaccuracy of the indirect method for determining the presence of virus

The fixed-cell tube culture

1. *The roller-tube culture* The roller-tube culture was first adapted to the cultivation of a virus by Gey & Bang[14] in 1939 and to the propagation of the poliomyelitis viruses in 1950 by Robbins, Enders & Weller.[36] The technique originally employed by the latter investigators has been described at length[38] Others as well as ourselves[7, 22, 29, 48, 58, 60] have subsequently introduced certain modifications, particularly with respect to the kind of tissue and fluid media employed

In contrast to the suspended-cell culture, the roller tube allows the cytopathogenic effect of the virus to be directly visualized under the low power of the microscope This is a great advantage since multiplication

roller-tube cultures of this tissue are less sensitive in infectivity assays and give lower yields of virus than comparable cultures of monkey kidney tissue. In view of this finding, and also of the fact that monkey kidney material is available in much larger quantities, testicular tissue has been less widely employed of late

2. *The stationary culture* Rolling of tissue cultures was first introduced because it enhanced the growth of cells and permitted of their maintenance for long periods of time without the frequent necessity of explantation Long before this procedure was introduced, however, cells embedded in a plasma matrix were successfully grown in stationary cultures This technique has been shown to be suitable for the propagation of the poliomyelitis viruses by Li & Schaeffer,[23] Scherer & Syverton,[46] and Melnick & Riordan[25] and their co-workers The preparation of the cultures is essentially the same as for roller-tube cultures, except that about six fragments of tissue are embedded in a row on one side of the tube in a streak of plasma After the addition of the medium, they are inclined at an angle (5°) that permits the fluid to cover the fragments and extend a little beyond them. Titrational end-points and viral yields in stationary cultures of this sort appear to be approximately equivalent to those obtained in roller-tube cultures Close inspection of Melnick & Riordan's results,[25] however, suggests that somewhat higher quantities of virus are more regularly obtained when the cultures are rolled. It is doubtful whether these slight differences are sufficiently important to warrant the purchase of the apparatus required for rolling the cultures if this is not already available

Within the past year (1953-4) stationary cultures in which no plasma is included have been used for the cultivation of poliomyelitis virus. By pre-heating the tube to 45°C before the tissue fragments are introduced, Morann & Melnick[20] have shown that the tissue fragments can be made to adhere to the glass when the medium is subsequently added From fragments of monkey kidney treated in this manner an outgrowth of cells occurs, which in turn remains adherent to the glass Such cultures can be easily and rapidly prepared in large quantities and have been found satisfactory for titration of infectivity as well as for virus-neutralization tests

Comment on the applications and relative merits of the rolled and stationary cultures of this type will be deferred until after the description of the trypsinized-cell cultures.

The trypsinized-cell culture of Dulbecco

An important technique has been developed by Dulbecco & Vogt[5] for the precise determination of the number of infective particles of a

consisting mostly of epithelial elements that are *extremely sensitive* to the destructive action of the virus Moreover, the quantity of virus developing in kidney cultures is as great as, or greater than, that emerging in cultures of other tissue types The sensitivity of kidney tissue in supporting the growth of very small viral inocula has also been found to be equivalent to, or to exceed, that of other types For the isolation of poliomyelitis viruses from suspensions of human faeces, cultures of human kidney epithelium have proved superior in our hands to those consisting of human myometrium or embryonic skin and muscle Their superiority is due partly, at least, to the fact that the cell outgrowth is less sensitive to the toxic factors which, in varying degree, are present in faecal preparations (see page 287) Monkey renal tissue also appears to share these advantages In recent unpublished experiments, however, we have found that cultures of monkey kidney tissue are somewhat less sensitive than those of human kidney in revealing the presence of minimal quantities of virus in stool specimens Thus, following the inoculation of 1 ml of 10%-stool suspensions from 16 patients with poliomyelitis which were known to contain only small amounts of virus, the agent was recovered from 15 when tested in cultures of human cells and from 8 in cultures of rhesus-monkey cells When suspensions containing large quantities of virus were examined such differences were not observed Another disadvantage inherent in the use of monkey cells would seem to consist in the fact that occasionally, as we and others have found, they may be contaminated by viruses indigenous in the monkey Possible contamination, therefore, of the cultures with agents derived from the monkey itself must be constantly borne in mind if the tissues of this animal are employed

The difficulty of obtaining sufficient supplies of human kidney render it unsuitable for routine use by most laboratories As a *substitute, if it* is desired to employ human cells, uterine tissue has been found to be reasonably satisfactory [38] This is obtainable in any large hospital, and produces, in roller-tube cultures nourished with the bovine-amniotic-fluid medium, a good growth of cells after about 10 days' incubation at 37°C Although somewhat better growth may possibly be obtained with tissues removed from women before the menopause, postmenopausal material has proved adequate in our hands Another substitute for human kidney is to be found in human preputial tissue removed by circumcision Although at an early stage difficulty had been encountered in regularly propagating poliomyelitis viruses in suspended cell cultures of this tissue, we have lately obtained consistent results in roller-tube cultures of prepuce in which both fibroblastic and epithelial cells emerge and are destroyed by the virus.

In the past, extensive use has been made of monkey testicular tissue by various workers More recently, however, it has been determined that

prepared in this way from the renal tissue of one monkey. Using these cell suspensions, cultures in flat-sided bottles (40 mm × 110 mm) have been successfully established and applied to the propagation of larger quantities of virus

The medium employed by Youngner during the growth phase consists of a slightly modified form of Mixture No. 199 (98%) and normal horse serum (2%). At the time when the viral inoculum is introduced, Mixture No 199 alone is substituted with the purpose of eliminating the possibility of including virus-inhibiting factors that may be present in certain lots of horse serum. We have recently prepared cultures of trypsinized human kidney tissue as well as of monkey kidney tissue by the method just outlined and have found them satisfactory for titration of poliomyelitis virus and for serum-neutralization tests With the exception of monkey testis, which in Dulbecco's hands yielded cultures that varied considerably in their suitability for making plaque counts, human kidney so far has proved to be the only other tissue that can be used in this manner In our laboratory we have subjected human thymus and spleen to the same procedure, either no satisfactory cell suspensions were obtained or the cells failed to enlarge and form continuous sheets

Comment on fixed-cell cultures of primary explants

All of the various types of fixed-cell cultures just reviewed are for most purposes to be preferred to the suspended-cell culture since they afford direct criteria for the multiplication of the poliomyelitis viruses Among themselves, however, it is at present difficult to select one that combines the advantages of all and which therefore might be recommended for adoption as standard From the standpoint of ease of preparation and economy of materials the trypsinized-cell tube culture seems at the moment to be pre-eminent and indeed approaches the ideal system provided sufficient quantities of human or monkey renal tissues were everywhere available But this is not the case in certain areas of the world Under such circumstances the fixed-cell plasma cultures of certain human tissues (embryonic skin-muscle or lung, post-natal prepuce or uterus), stationary or rolled, should be used

The choice of media will also in part depend upon the readiness with which certain materials can be obtained Mixture No. 199, or modifications thereof, has the outstanding advantage of known composition which ensures uniformity of successive lots When reinforced with horse serum, it appears to support growth of cells Used alone, however, it fails to provide the necessary factors for continued multiplication, and spontaneous degeneration of cells may ensue after a time. Since routine tests with poliomyelitis virus can be accomplished within from five to seven

cytopathogenic virus that may be *present in a given suspension. Their* method consists in establishing a continuous monolayer of tissue cells (monkey kidney or testis) on the bottom of a Petri dish. The cells are then exposed to a high dilution of the suspension of virus. After a short interval they are covered with a nutrient agar mixture which serves to localize the virus in the areas in which infection of individual cells has taken place Multiplication of virus is followed by destruction of adjacent cells This effect becomes visible within 24-48 hours and resembles the plaques formed by bacteriophage in confluent agar cultures of bacteria. Dulbecco has presented convincing evidence indicating that a plaque is caused by a single infective virus particle The method, therefore, provides an extremely accurate means of assay for viral infectivity and possibly for measurement of antibody concentration. Moreover, it offers a simple way of obtaining pure-line strains and so of studying viral mutation, since virus-containing material composed of the descendents of a single infective "plaque unit" may be easily removed and employed as inoculum for *serial passage*

From the practical point of view, the technique devised by Dulbecco for obtaining the continuous monolayer of cells is of great value since it also affords a convenient and economical means of securing a suspension consisting of single cells or small clumps of cells that, as Youngner [59] has shown, may be quantitatively evaluated and used for the preparation of stationary-tube cultures.

The procedure as modified by Youngner is in outline as follows. The cortical area of a kidney from a rhesus or cynomolgus monkey is minced The minced tissue, after being washed in buffer solution, is treated with trypsin solution at 37°C After a short interval the solution is discarded and fresh solution added Digestion is allowed to proceed for the same length of time while the suspension of tissue is gently agitated in a Waring blendor, the speed of which is controlled by a rheostat After the fragments have settled, the supernatant fluid is removed and the coarse material it contains is separated by filtration through gauze. This procedure is repeated until nearly all the cells have been separated from the tissue. The aliquots of trypsinized suspension are pooled and centrifuged, and the cells washed with the nutrient medium employed for their cultivation From the packed cells a suspension is prepared which is used for standardization This is accomplished by determining the number of cells by counts of the nuclei or of the optical density For use in tube cultures,

[illegible]

horizontal)

ultimately forming a continuous layer. After six or seven days the cultures are ready for inoculation. From 800 to 1,000 cultures have been

Techniques for propagation of HeLa cells

The HeLa strain was derived by Gey and his collaborators from an epidermoid carcinoma of the cervix It has been maintained in continuous, serial, culture passage up to the present time The cells grow readily on a glass surface and multiplication is rapid The manner in which these cells can be applied to the cultivation and study of the poliomyelitis viruses has been described in detail by Scherer, Syverton & Gey [47] and Syverton, Scherer & Elwood [54]

The essential steps in the procedure for the cultivation of these cells are as follows Stock cultures may be maintained conveniently in square bottles of about 200-ml capacity Cell growth is allowed to proceed on one side of the bottle, which is incubated at 37°C in the horizontal position About 6 ml of growth-promoting medium (see below) cover the layer of growing cells When sufficient growth has occurred (usually after from seven to ten days) it is removed by means of a bent glass-rod The mass of cells is then treated at 37°C with 8 ml of 0 5% trypsin solution for a total period of 90 minutes, at the end of one hour the suspension is agitated to break up cell clumps The suspension, which now consists mainly of single cells or small aggregates, is centrifuged at 1,000 revolutions per minute (r p m) and the cells taken up in nutrient medium After the number of cells per ml has been determined in a blood-counting chamber, the suspension is adjusted so that from 25,000 to 100,000 cells are added to test-tubes (16 mm 150 mm) containing from 0 5 ml to 1 5 ml of the growth-promoting medium (see below) The tubes are slanted at approximately 5° and incubated in a stationary position at 37°C After two or three days the medium is replaced either entirely or in part by fresh material The cultures are usually ready for use from the 3rd to the 7th day thereafter

An alternate method omits the use of trypsin When followed, this technique consists in scraping off a portion of the cellular growth from the wall of the vessel This is cut into small fragments, which are placed on the wall of a culture vessel that has previously been wetted with the medium. After a short interval (10 minutes) the fragments become sufficiently adherent to permit of the addition of the complete supply of nutrient medium

Two media of different composition are successively employed in the use of these cells for studies on poliomyelitis viruses The first, which affords the necessary factors for active cell-multiplication, consists of a mixture of either human placental serum, human adult serum, or human ascitic fluid (50%), chick embryonic extract (2% or 5%), and balanced salt solution (Hanks' solution,[18] 48% or 45%) For the maintenance of the

days, this incompleteness of the medium is not usually significant. If, however, it is desirable to study the effect of the virus over a longer period (for example, in safety tests for supposedly inactivated viral suspensions), it would seem advisable to adopt a complete medium, such as Mixture No 199, with the addition of serum or amniotic fluid and of embryonic extract. When such media are employed it is essential to determine whether the ingredients—in particular the serum—contain factors that may inhibit multiplication of small inocula of virus.[38]

Synthetic media even when supplemented with serum have, theoretically at least, an additional advantage since there is far less likelihood of their being contaminated with a "wild" virus than in the case of media composed of embryonic extract and such materials as amniotic fluid So far, however, in several thousands of cultures of various human tissues in which the latter ingredients have been incorporated, we have encountered no indication of the presence of such agents. Nor have we evidence for the presence of *Brucella abortus* as a contaminant Even if this organism were present it might be expected that treatment with streptomycin would inhibit its growth or destroy it.

The chief disadvantage of synthetic media such as Mixture No 199 lies in the large number of different ingredients required These are sometimes difficult to obtain and render the preparation time-consuming and laborious. In certain laboratories, where many cultures are continuously required, these difficulties are readily overcome However, in laboratories where smaller numbers of cultures are used or where certain of the ingredients may not be easily procured, media composed of the crude biological materials already mentioned should afford satisfactory substitutes When it is desired for special purposes, such as the preparation of complement-fixing antigens,[50] to produce suspensions of virus relatively free from foreign proteins, the complete medium may be replaced by one consisting of Hanks' balanced salt solution (75%) and bovine serum ultrafiltrate (25%) at the time the virus inoculum is introduced

Techniques Included in Group II

Although various strains of animal cells maintained under continuous cultivation in vitro have been employed in the propagation of certain other viral agents, so far only the HeLa strain of human carcinoma cells has been applied to any extent in the propagation of the poliomyelitis viruses. There is, however, evidence that strains of normal and other malignant human cells also provide suitable media for the propagation of these agents.

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cells without proliferation after inoculation of the virus, a mixture of a synthetic solution[45] and chicken serum—consisting of nine parts of the former and one part of the latter—is substituted. The volumes of these media which are employed and the frequency with which the media are changed depend upon the size of the vessel and the number of cells Large cell-populations reduce the pH of the medium, rapidly necessitating more frequent changes of media At the time of inoculation of the virus the complete medium is removed and the culture washed once or twice with the maintenance medium The latter is then used as long as the cultures are preserved

Technique for maintenance of normal human cells in continuous culture

Swim & Parker[52] have recently described methods whereby they have been able to maintain stocks of various normal human cells in culture over a period of about six months For this purpose two procedures were employed after the original cultures had been established. The original cultures consisted of roller-tube cultures in which precautions were taken to ensure the growth of cells within a very thin clot This result was obtained by using small quantities (0 05 ml) of chicken plasma and chick-embryo extract and removing the excess fluid before clotting occurred After cell growth was well established, the original fragments of tissue were removed, leaving the sheets of new cell-growth on the wall of the vessel Cells were observed to grow over the glass surface exposed by contraction of the clotted plasma

From this point on, two procedures for the continued cultivation of the cells were followed In the first, the initial cell-growth was sub-cultured by removing a portion of the cells with a bent platinum-wire The mass of cells suspended in a portion of the medium was broken up to form a suspension of single elements and small clumps by drawing them in and out of a serological pipette. After centrifugation and removal of the fluid, the cells from several cultures were suspended in a small volume of embryonic extract and in this form spread over the lower portion of the wall of tubes that had been previously coated with a thin film of plasma as in the preparation of the ordinary roller-tube culture Serial cultures were carried out in this manner over a period of six months, during which cell growth continued in a satisfactory manner.

The second procedure consisted in preserving the original cultures by the addition of fresh media and by continued incubation after the removal of a portion of the cells for the first of the serial explants. Multiplication of the cells in the original cultures continued, again covering the wall of the tube. The new growth was largely removed and used to prepare cultures

for inoculation with virus This operation was repeated many times The establishment and maintenance of such "mother cultures" would seem to provide a convenient source of cells over an indefinite period

Cells cultivated for six months according to these techniques were found to exhibit the usual degenerative changes following the addition of poliomyelitis virus Successful results were obtained with a variety of human tissues that included adult human uterus and testicle and embryonic skin-muscle, liver, lung, and kidney

The medium used for propagation of these various cell-types consisted of Fischer's V-164 solution[11] (85%), normal horse serum (10%), and embryonic extract (5%) Chick and beef embryonic extract were each employed in different experiments At the time of inoculation of the virus this medium was replaced by Medium No 199 For cultivation of most cell-types the beef embryonic extract appeared to provide the most satisfactory conditions for growth

Comments on use of cells under continuous cultivation

It is clear that the ideal system for the propagation and study in vitro of the poliomyelitis viruses, as well as for other agents of this class whose growth appears to be restricted to primate cells, would consist of a "pure" strain of normal human cells—preferably one initiated from a single cell Furthermore, all requirements for the perfect culture would be fulfilled if a cell line of this sort could be maintained in a medium of chemically known composition Such a system, once suitable tests were carried out, would ensure the absence of possible contaminating viruses (for example, the agents of infectious hepatitis, or the agents that may appear in cultures of monkey tissues from time to time). It would also be free of the theoretical objections raised against the use of malignant cells in materials that might be inoculated into human beings The results of all operations would presumably be rendered more accurate and reproducible because of the uniformity of the elements composing the cultures, provided no biological changes in the cell line occurred that might affect the susceptibility of the cells to the virus under investigation

At present no culture of this type is available However, the successful application of the types of continuous-cell cultures that have just been described, together with the most recent developments in the search for a synthetic medium furnishing all requirements for cell growth, encourage the hope that the ideal combination may become a reality in the not-distant future

In the meantime, it is evident that the existing techniques for the continuous cultivation of cells have definite advantages as well as disadvantages

when compared with techniques employing only the cells from original explants HeLa cells have the merit of apparently consisting of a single type of cell which can be cultivated in large quantities with relative ease Most stocks appear to be highly sensitive to the cytopathogenic effect of the viruses, although there have been indications that lines carried in certain laboratories have developed increased resistance to poliomyelitis virus The yields of virus obtained in the presence of fully susceptible HeLa cells compare favourably with those obtained in cultures of monkey or human renal cells The ease with which replicate cultures may be prepared containing initially the same number of cells represents a distinct advantage over cultures in which tissue fragments are used. In this respect, however, there is little choice between trypsinized kidney and HeLa cell cultures

The chief advantage of the Swim-Parker method seems to consist in the simplicity with which stocks of various *normal* human cell-types may be established for long periods of time As yet no techniques for accurate quantitation of the cells have been described, although it would seem that trypsinization might be invoked successfully as in the case of HeLa or renal epithelial cells Whether large stocks of normal cells sufficient for routine large-scale infectivity, virus-neutralizing tests, or vaccine production can be maintained continuously has not been determined, but this seems a likely possibility

The principal difficulty encountered in the use of HeLa cells lies in their dependence for active multiplication on factors present in human serum or ascitic fluid Large supplies of these materials are frequently inconvenient or costly to obtain Moreover, certain specimens appear to be more suitable than others for the promotion of cell growth Since these human products often contain neutralizing antibodies for the poliomyelitis viruses, media containing them must be eliminated before these agents are inoculated The procedure is thus complicated by the necessity for employing as routine two types of medium. While the cytopathic changes induced by the poliomyelitis viruses are usually unequivocal, in HeLa cells we have occasionally encountered difficulty in deciding whether or not certain degenerative manifestations were to be attributed to this cause or to non-specific factors This situation has arisen most frequently when limiting viral inocula have been added, and has necessitated subculture to verify the specific nature of the observed changes In this respect the cytopathogenic effects on renal or uterine cells are, in our opinion, more characteristic and unequivocal

HeLa cells appear to be more sensitive to the toxic action of certain faecal suspensions than are either monkey or human kidney cells Thus,

in comparative unpublished experiments in which we have employed varying quantities of human faecal suspensions as inocula, rapid rounding and death have ensued more frequently and with smaller quantities of inoculum in cultures of the malignant cells as contrasted with those of monkey or human epithelium Accordingly, when HeLa cells are employed for the isolation of poliomyelitis virus, Syverton and his co-workers[54] have recommended a procedure involving centrifugation at 15,000 r.p m and inoculation of the supernatant fluid If renal cells are used (S. Kibrick and J F. Enders—unpublished observations) the crude suspension may, in the large majority of cases, be added directly to the culture without causing cell injury sufficiently severe as to interfere with observations on the cytopathogenic effect of the virus

Finally, two other considerations already alluded to should be kept in mind respecting HeLa cells First, the possibility of variation in their susceptibility to the virus must be remembered and appropriate tests frequently carried out to eliminate its occurrence. Secondly, HeLa cells would seem unsuitable as a substrate for the production of poliomyelitis vaccine Although it is improbable on the basis of present knowledge that the injection of cell-free solutions in which the HeLa cells had multiplied would lead to neoplastic changes, one still remains reluctant to inoculate these materials into human beings since not enough is yet known concerning the causes of cancer to warrant taking what seems to be even a minimal or merely theoretical risk involved in a procedure of this nature

Few data are available on the cells grown according to the method of Swim & Parker as applied to routine procedures now in use for poliomyelitis virus It is, therefore, impossible to discuss satisfactorily the merits of the technique The advantage of having constantly available lines of normal human cells has already been indicated. Provided these can be preserved in a state susceptible to viral attack and grown in sufficient quantities, they would seem to offer the most desirable medium for the propagation of the poliomyelitis agents At times, however, resistant cell-populations may arise Thus, in our own recent and unpublished attempts to develop such stocks, one line of cells originating from human embryonic skin-muscle fragments was found to have become completely refractory to inoculation of representatives of all three prototype strains of poliomyelitis virus Neither cytopathic changes nor multiplication of the agents followed their addition to cultures composed of these cells. It also remains to be seen whether or not lines of normal human cells can be extended indefinitely in tissue culture, since in the past various workers have noted that the capacity to undergo continuous multiplication in vitro may be lost after a time Furthermore, it is possible that under prolonged cultivation changes may occur resulting in the emergence of malignant cells

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If a sufficient number of cultures are inoculated with each dilution of the suspension of virus, the 50% infective dose—as indicated by the dilution of virus that produces cytopathic changes in one half of the cultures inoculated—can be calculated according to the method of Reed & Muench [34] The minimal number of cultures required to determine this value within a reasonable degree of accuracy is three It is of course obvious that accuracy may be increased by the use of a larger number of preparations and of dilution intervals of one half log instead of one log. For special purposes certain workers have employed as many as ten cultures, but for routine work three have, in our hands at least, proved satisfactory

Comparative experiments have shown that when strains of maximal virulence for experimental animals (monkeys or mice) have been titrated in vitro and in vivo the end-points of viral infectivity are usually comparable However, since under certain conditions virulence for animals may decline while infectivity for tissue-culture cells may remain constant (see pp 290-291), such agreement is not always found,[9, 58] moreover, when a strain of virus has been propagated in an animal it may, when first introduced into tissue cultures, appear less infective or at least exhibit a delayed or incomplete cytopathogenic effect Usually one or two passages in vitro will re-establish maximal cytopathogenicity Occasionally a virus, such as the Lansing strain, may be encountered which, even after continued passage, remains only moderately cytopathogenic [21]

Isolation of Virus from Man and Experimental Animals

With the advent of antibiotics the application of tissue-culture techniques to the isolation of viruses from materials heavily contaminated with bacteria was made possible Up to that time the only method available for the elimination of bacteria in the discharges or secretions of patients or animals consisted in filtration This procedure is known to remove varying proportions of the virus even under optimal conditions, it often proved unsatisfactory, therefore, in attempts to isolate these agents, especially when they were present initially in low concentration

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SUMMARY OF APPLICATIONS OF TISSUE CULTURES TO STUDY OF POLIOMYELITIS VIRUSES

As was remarked at the beginning of this article, tissue cultures have, during the last four years (1950-4), been applied in a variety of ways to the study of the poliomyelitis viruses For purposes of easy reference, I shall summarize here under appropriate headings the principal contributions in this field

Assay of Infectivity

The first application of the tissue-culture method to the assay of viral infectivity was made in suspended-cell cultures employing a difference in pH between inoculated and control cultures as the criterion for viral activity [36, 56]

When it was shown [36] that the cytopathogenic effect could be more readily and accurately observed in roller-tube cultures this method was extensively used for a time by various investigators [22, 38, 44, 58, 60] The procedure simply consists in introducing a measured volume of inocula (usually 0 1 ml) from each of a series of graded dilutions of the virus suspension into two or more roller-tube cultures of a suitable tissue. The relative sensitivity of various sorts of cells to the virus has been indicated in the sections on tissue-culture techniques It is customary to employ cultures in which a well-developed outgrowth of cells has been obtained after preliminary incubation At frequent intervals after the virus is introduced, the cultures are examined for the presence of degenerative changes in the cells Their appearance is variable depending upon the kind of tissue and the quantity of virus Thus, for example, cytopathic changes are manifest earlier in human renal epithelial cells than in human uterine cells Such changes may also become apparent in human renal cells 24 or 48 hours before they can be definitely discerned in monkey cells of the same type Large doses of virus—for example, 1,000 50% tissue-culture-infecting doses of virus (ID_{50}) or more—induce a cytopathogenic effect within 24-48 hours.

With very small inocula this may not be visible until the 5th to the 7th day, and in rare instances may be delayed for as long as 10-14 days Most investigators, however, have taken final readings of titrations for infectivity on the 5th or 7th day. Except in the case of titrations to determine virus-inactivation during the preparation of vaccine, this test period would seem to yield results of reasonable accuracy.

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Robbins et al.[37] Suspended-cell cultures were employed except in one case in which evidence was obtained that virus could be isolated and typed simultaneously in roller-tube cultures. Since then reports have appeared which include altogether summaries of the isolation and serological typing of over 600 strains of poliomyelitis virus by means of tissue-culture techniques.[51] Suspended-cell cultures, roller-tube cultures, and stationary fixed-cell cultures have all been employed, as well as different kinds of human and monkey cells. Syverton and his co-workers, using HeLa cell cultures, have so far reported the largest number of isolations. The details of their method have recently been made available.[47, 51]

In plasma roller-tube cultures of human embryonic skin-muscle and mature human uterine and renal tissues, Kibrick, Enders & Robbins have isolated 157 strains from the faeces of 211 cases of paralytic and non-paralytic poliomyelitis. Most of the data have not yet been published in extenso. A single specimen of faeces from each patient was tested. The proportion of isolations as correlated with the clinical diagnosis was as follows:

Clinical diagnosis	Number of cases examined	Number of viruses isolated	Isolations (%)
Paralytic	121	119	98
Non-paralytic	90	38	42

The procedure employed for the isolation and typing of the majority of these strains was essentially as follows. Crude faecal specimens were stored at −15°C until used. For inoculation of the tissue cultures a 10% faecal suspension was prepared, in beef-amniotic-fluid medium containing 100 units of penicillin and 50 μg of streptomycin per ml, by grinding in a mortar. The suspension was centrifuged at 4,000 r.p.m. for one hour in an angle head (Sorvall). The clearest portion of the supernatant fluid was used as inoculum. 0.1 ml was added to a roller-tube culture containing 2 ml of beef-amniotic-fluid medium. Cultures were examined during an interval of 10-14 days unless a cytopathogenic effect had been earlier observed. When this effect became evident, aliquots of the supernatant fluid diluted 1/10 in phosphate buffer-solution were mixed with an equal volume of an antiserum prepared in monkeys against representatives of each of the three prototype viruses. The antisera were diluted 1/3 or 1/5 before they were mixed with the virus. The virus-antiserum mixtures were allowed to stand at 2°-4°C for one hour, after which 0.2 ml of each was added to a tissue culture. The cultures were examined at frequent intervals until degeneration was evident, or for one week. In the rare instances when inhibition of cytopathogenicity failed to occur in any of the three cultures, the virus suspension was diluted 1/100 or 1/1,000 and the typing procedure repeated.

When no evidence of the presence of virus was obtained in the initial attempt at isolation using 0 1 ml of the faecal suspension, larger inocula were employed ranging from 0 5 ml to 3 ml Not infrequently these amounts proved toxic to the tissue cells, as was indicated by rounding, disintegration, or disappearance within a few hours. This effect could be minimized or eliminated by (*a*) shorter exposure of the cells (from 30 to 60 minutes) to the faecal suspension, which was then removed and replaced by fresh medium; (*b*) continued incubation for 24-48 hours and transfer of the supernatant fluid (1 0 ml) to a fresh culture with one-hour exposure, and (*c*) the use of kidney cells instead of embryonic or uterine cells, since kidney cells have proved more resistant to the toxic effect of the faecal suspension

The time required for the isolation and serological identification of poliomyelitis virus could be reduced by employing the faecal suspension instead of the infected tissue-culture fluid in the procedure for the determination of the antigenic type previously described In addition to the three cultures inoculated with mixtures consisting of the faecal suspension and each of the three type-specific antisera, a fourth culture was inoculated solely with the faecal suspension diluted 1/2 in phosphate buffer-solution When simultaneous isolation and typing was attempted in this manner, it was found best to use cultures of kidney tissue in order to reduce the risk of encountering the toxic effect produced by some faecal specimens

At present, cultures of either HeLa cells or kidney cells (roller-tube or stationary cultures of trypsinized cells) would seem to be preferred for the isolation of poliomyelitis viruses The principal advantage of the kidney over the HeLa cell lies in the fact that it appears to be more resistant to faecal cytotoxins, thus enabling relatively crude suspensions of faeces to be employed as inocula

Assay of Virus-Neutralizing Antibody

The assay of virus-neutralizing antibody in tissue cultures has usually been accomplished by a procedure essentially comparable to that just described for the determination of the antigenic type [20, 61] A series of suitable dilutions of the serum is prepared and each dilution is mixed with a known quantity of virus previously determined by titration It has recently been the practice of most investigators to employ 100 ID_{50} Smaller amounts may be used but irregularities begin to be noted if less than about 30 ID_{50} are added The virus-serum mixtures are maintained at 2°C to 6°C for one hour and 0 1 ml or 0.2 ml is inoculated into each of three or more cultures of either the roller-tube or stationary type Appropriate control cultures to which the virus suspension alone is added, as

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For these reasons, the test appeared to be of limited value from the practical diagnostic point of view and could be regarded as of only auxiliary value as an epidemiological tool Recently, however, certain modifications give promise of enhancing its usefulness in these respects In the first place, it has been found by various workers, including ourselves, that with certain strains of viruses cultivated under optimal conditions antigen is released into the fluid phase of the culture in sufficient amounts to permit of its use in the complement-fixation test without recourse to concentration Secondly, investigations by Black & Melnick [1] on the effect of varying the concentration of the various reagents involved in the test indicate that under carefully controlled conditions a much larger proportion of monotypic reactions can be obtained with the sera of poliomyelitis patients

The technique of preparing the concentrated antigens from tissue-culture fluids has been described in detail by Svedmyr and his associates. Unconcentrated fluids from cultures of human and monkey kidney tissues nourished with the beef-amniotic-fluid medium or Medium No 199 have been used by ourselves and by Black & Melnick Those who have employed antigens derived from tissue culture have generally adopted the "plate" or "drop" technique in carrying out the complement-fixation test This procedure, originally described by Fulton & Dumbell,[13] has been slightly modified by those who have applied it to studies on poliomyelitis Its chief advantage lies in providing a great saving of materials —both reagents and glass-ware

Tissue Cultures in Studies on Factors Involved in Viral Multiplication

Because the tissue culture provides a system that is relatively simple compared with the living animal, it has lately been frequently invoked in attempts to define some of the biochemical factors concerned with viral multiplication Brown and his associates have studied the effect of certain analogues of amino acids, purines, pyrimidines, and vitamins on the growth of poliomyelitis virus in suspended-cell cultures [2, 3] In certain instances where apparent inhibition of viral multiplication occurred after addition of an analogue, this was reversed by the addition of the corresponding metabolite Since it had been previously shown by others [55, 56] that acid production was reduced in cultures infected with the virus, Franklin and his co-workers [12] made quantitative determinations of the utilization of glucose at various intervals following inoculation of the virus They concluded that the amount of glucose used by cultures containing virus is significantly less than that used by uninoculated control cultures. Tissue cultures have been applied by Hull & Lavelle [17] to the analysis of the mode of action of a mould filtrate, designated M-8450, that had been

well as other cultures receiving the lowest dilution of serum to be tested, should be included "Readings" are taken after an arbitrary period of incubation With 100 ID_{50} of virus this period has been fixed at four or five days by certain investigators.[20] If longer intervals are chosen, lower antibody titres may be recorded because of a tendency for the cytopathogenic effect to appear or "break through" after a delay in cultures receiving higher dilutions of serum

The virus-neutralizing capacity or titre of the serum is calculated according to the method of Reed & Muench[34] and is recorded as the highest dilution of serum which prevents the development of cytopathic changes in half of the cultures to which it has been added.

As noted previously (see pp 284-285), the end-point of neutralization may be determined in suspended-cell cultures by observing differences in pH of the medium in a titrational series Salk has recently shown that this method is simple and rapid when a system consisting of trypsinized monkey kidney cells suspended in Medium No 199 is employed (see page 284, footnote *c*) Further experience with this technique will, however, be required before it can be recommended as a standard procedure.

Tissue Cultures as a Source of Antigen for Complement-Fixation Tests

Casals, Olitsky & Anslow[4] were the first to develop an antigen that could be applied practically in complement-fixation tests for poliomyelitis antibody. This material consisted of an acetone extract of mouse brain infected with type 2 virus Since type 1 and 3 antigens could not be prepared in this manner, Svedmyr and his co-workers[50, 51] investigated the possibility of using the infected fluid from tissue cultures in which these agents had been propagated In their early experiments it was found that the crude fluid did not contain sufficient antigen to be used in this manner. Consequently, infected fluids were concentrated from 100 to 500 times by a simple method of dialysis[50] The concentrates were found to fix complement in the presence of anti-poliomyelitis monkey sera as well as of sera taken from patients with the disease Whereas antigens representing *the three prototype strains of virus reacted specifically with their homo-*
[illegible] han the latter were derived from the monkey they exhibited

characteristic of the monkey sera In certain instances significant increases in complement-fixing antibody could be demonstrated during the course of poliomyelitis in man, but frequently this antibody had apparently attained its maximum at the time when the first specimen of serum was obtained.

and then with human beings[41, 42] were undertaken by Salk to determine whether tissue-culture fluids treated with formalin might likewise be immunogenic. This proved to be the case, as was indicated by the development of neutralizing antibodies in the majority of vaccinated subjects. At present in the USA a large-scale experiment is in progress to ascertain whether a polyvalent vaccine developed by Salk, consisting of representatives of the three prototype strains grown in monkey kidney tissue and Medium No 199 and inactivated by incubation at 36°-37°C in the presence of formalin, will confer protection against natural exposure to poliomyelitis. Recently Milzer and his associates[28] have reported that tissue-culture virus inactivated by ultraviolet irradiation also exhibits antigenic properties when inoculated into man Because of their apparent efficiency as stimulators of antibody, the absence of nervous-tissue elements, and the very low content of extraneous proteins, vaccines prepared from tissue-culture fluids appear to offer promise of being satisfactory prophylactic agents

Tissue Cultures as Means of Studying Viral Mutations

In spite of occasional evidence suggestive of variation, the general impression in the past has been that the properties of the poliomyelitis viruses, especially that of pathogenicity, were, relative to certain other agents of this class, unusually stable Of late, observations made on strains propagated in tissue culture have shown that this conception was wholly unfounded Early in our studies we noted that a significant decline in virulence for mice occurred after repeated passage of the Lansing strain (type 2) in suspended-cell cultures of human embryonic tissues [56] Although in this instance virulence could be quickly restored by passage in mice, it was clear that temporary loss of pathogenicity had indeed occurred since the end-point of infectivity as determined in vitro remained constant at all times Serial passage of the Brunhilde strain (type 1) in suspended-cell cultures similarly resulted in a reduction of virulence for the monkey[8] Additional passages in roller-tube cultures employing the "end-point dilution" technique quickly resulted in a further depression of pathogenicity Thus 10^5-10^6 ID_{50} for tissue cultures in most instances failed to induce paralysis when introduced into monkeys by the intracerebral route This attenuated strain has proved to be more stable than the Lansing variant mentioned above Sabin (personal communication), however, has recovered a virus of high intracerebral virulence from the spinal cord of a monkey that had become paralysed after inoculation with this attenuated Brunhilde strain Obviously, therefore, fixation of virulence in the Pastorian sense has not in this case been achieved. Working with other strains

shown in vivo by others to possess antiviral properties In vitro it was necessary to add the filtrate several hours before the virus was inoculated in order to prevent the appearance of cytopathic changes. Since no direct effect of the filtrate on the virus could be demonstrated, the authors concluded that this material exerted its effect on the cells.

Although at present published investigations dealing with the factors involved in the multiplication in vitro of poliomyelitis viruses are few, it can be predicted with confidence that their number will increase rapidly in the future since the tissue culture provides the simplest system available for the analysis of these factors. The use of known numbers of cells of a "pure" line maintained in a synthetic medium should be of material aid in researches of this sort

Role of Tissue Cultures in Purification of Poliomyelitis Viruses

It is now possible to produce large quantities of all strains of poliomyelitis virus in tissue cultures in which the only materials of undefined chemical composition present are the viruses themselves and those materials derived from the cells This situation obviously facilitates the preparation of purified suspensions of these agents to be employed in studies of their biochemical and biophysical properties

Already reports from Sabin and his co-workers[39] indicate that purified suspensions may be easily obtained from the fluid of infected tissue-cultures, which largely consist of particles of a size compatible with that of the poliomyelitis viruses as derived from infected nervous-tissues. It would seem likely that future technical modifications—such, perhaps, as enzymatic digestion of viral suspensions partially purified by differential centrifugation—should yield preparations consisting entirely or almost entirely of the virus itself

Tissue Cultures as Sources of Antigens for Preparation of Vaccines

Shortly after the demonstration that poliomyelitis viruses could be propagated in cultures of extraneural tissues, it was shown by Milzer et al[27] and by Enders[6] that the untreated fluids from cultures infected with the Lansing strain following intramuscular or intraperitoneal inoculation into mice established increased resistance to intracerebral injections of the homologous agent Since it had been found previously by others that inactive poliomyelitis virus in the form of infected formalinized monkey cord may give rise to immunity in various species of experimental animals,[19, 28] cotton rats,[24] and monkeys,[31] experiments first with monkeys[43]

and then with human beings[41, 43] were undertaken by Salk to determine whether tissue-culture fluids treated with formalin might likewise be immunogenic This proved to be the case, as was indicated by the development of neutralizing antibodies in the majority of vaccinated subjects At present in the USA a large-scale experiment is in progress to ascertain whether a polyvalent vaccine developed by Salk, consisting of representatives of the three prototype strains grown in monkey kidney tissue and Medium No 199 and inactivated by incubation at 36°-37°C in the presence of formalin, will confer protection against natural exposure to poliomyelitis Recently Milzer and his associates[28] have reported that tissue-culture virus inactivated by ultraviolet irradiation also exhibits antigenic properties when inoculated into man Because of their apparent efficiency as stimulators of antibody, the absence of nervous-tissue elements, and the very low content of extraneous proteins, vaccines prepared from tissue-culture fluids appear to offer promise of being satisfactory prophylactic agents

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representing all three antigenic types, Sabin and associates [40] have recently, by means of rapid passage (within 24 hours) in tissue culture by the end-point dilution method, obtained variants that produced no disease in monkeys which could be recognized either clinically or on histological examination of the nervous system. After intracerebral or extraneural inoculation from such strains, they have also segregated variants which are characterized by lack of cytopathogenic properties in cultures of both human and simian renal tissues but which exhibit a high degree of pathogenicity when inoculated intracerebrally into monkeys.

The theoretical, as well as the practical value of the study of variants of the poliomyelitis viruses is obvious Although it has only recently been pursued intensively, considerable progress has already been made. There is little doubt that knowledge of these phenomena will be rapidly extended by means of the methods now available Among the latter, Dulbecco's plaque technique, as previously indicated, should prove especially useful.

FINAL COMMENT

While it is hoped that this attempt to indicate how the tissue-culture method has of late years been effectively used to enlarge our understanding of the nature and behaviour of the poliomyelitis viruses, it is apparent that no technique has been devised that can as yet be selected for application as standard in all future investigations and as routine in laboratory diagnosis or in the preparation and assay of specific prophylactic agents Modifications are continuously being described—a fact that clearly reveals the " fluid " situation that exists in this area of research However, enough has been accomplished to support the belief that eventually a simple, accurate, and economical procedure will be established which for most purposes will be universally acceptable

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IMMUNOLOGY

IMMUNITY IN POLIOMYELITIS, WITH SPECIAL REFERENCE TO VACCINATION *

A B SABIN, M D

Professor of Research Pediatrics, University of Cincinnati College of Medicine, The Children's Hospital Research Foundation, Cincinnati 29, Ohio, USA

The purpose of this section of the monograph is to present a summary of the current status of our knowledge of immunity to poliomyelitis, as a consequence of natural infection in human beings, and of experimental infection and immunization in animals. Wherever possible, an attempt will be made to distinguish between the immune processes which prevent infection and those which prevent only the paralytic consequences of the infection [illegible]

ration of the epidemiology of the disease and the perpetuation of the poliomyelitis viruses in nature

A rational consideration of the various aspects of immunity in poliomyelitis became possible only after the demonstration, in 1951, that all the known strains of poliomyelitis virus from various parts of the world fell into three [illegible]

ty [illegible]
ot [illegible]
fo [illegible]
ha [illegible]

or major outbreak of clinically recognized poliomyelitis has as yet been found to be due to type 2 [13, 15]

IMMUNITY IN MAN

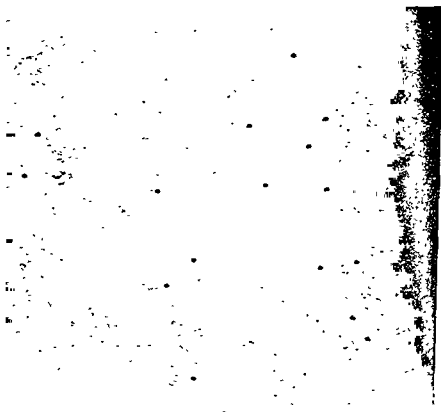
Antibody Response to Clinically Recognized Infection

Almost 40 years elapsed between the discovery of poliomyelitis virus and the demonstration that the antibody response in human infection followed the classical pattern observed in other virus diseases. The reason

* The studies on which this paper is based were aided by grants from the National Foundation for Infantile Paralysis Inc, N Y, USA

for this long delay is not only lack of knowledge regarding the multiplicity of immunological types, but perhaps even more the use of inadequate quantitative methods for demonstrating antibody, which postponed the realization that antibody for the infecting type of virus could be present at the

FIG. 1. TYPE 1 POLIOMYELITIS VIRUS (MAHONEY STRAIN)



Gold-manganin shadowed Magnification ×47,500

Reproduced from Sabin, A. B., Hennessen, A. & Warren, J. (1954) *Proc. Soc. exp. Biol. (N.Y.)* 85, 359 by kind permission of the editors

very onset of the clinical illness. For many years antibody tests were carried out with a few standard strains of virus, which we now know were predominantly type 2; when so-called "epidemic strains" were used, tests were performed with either undetermined amounts of virus or only the undiluted acute- and convalescent-phase serum specimens. It is not sur-

prising, therefore, that this gave rise to the dictum that in most poliomyelitis patients there was either no antibody in both the acute- and convalescent-phase sera, or that there was about the "same amount" in both [8, 10, 25] The first quantitative studies with strains of virus recovered

FIG. 2. TYPE 3 POLIOMYELITIS VIRUS (LEON STRAIN)



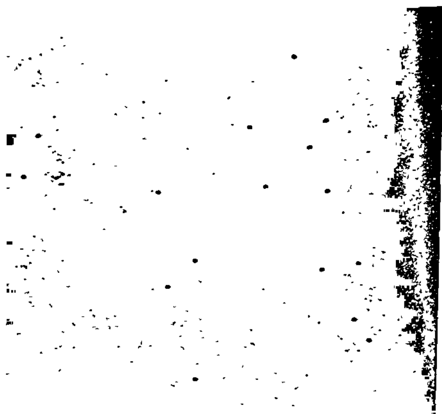
Gold-manganin shadowed Magnification ×47,500

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from the alimentary tract of the patients whose sera were being tested were carried out by Hammon & Roberts [23] and Steigman & Sabin [62] These studies, which were performed before the "tissue-culture era" at great cost in large numbers of monkeys, clearly showed that, with few exceptions, antibody for the infecting strain of virus was already present in the patient's

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which have not yet been fully investigated[14, 15, 67] (and unpublished data of A. B. Sabin & A. H. Fieldsteel), it would be of considerable interest to know whether or not the level of neutralizing antibody, as measured with the infecting strain and some standard homotypic strain, may vary at different times after a clinically recognized infection.

Antibody Response to Natural, Inapparent, or Subclinical Infection

The fact that the vast majority of the world population has been shown to acquire poliomyelitis antibodies without any recognizable clinical manifestations is now accepted as evidence of widespread infection with the poliomyelitis viruses, but by itself does not indicate that such antibodies were necessarily acquired without some sort of minor illness. Since the clinically recognized forms of poliomyelitis generally yielded high titres of antibody, and since the population at large exhibits a variety of titres, it is of some interest to know whether the antibody response to unrecognized infection is different from that observed in the recognized non-paralytic and paralytic disease The studies of Turner and his associates[63] provide information on both these points, in so far as type 2 poliomyelitis virus is concerned These investigators performed quantitative tests for type 2 poliomyelitis antibody on the sera of 24 Baltimore, USA, children, who had no such antibody before the "poliomyelitis season" but developed it during subsequent months, all without clinical evidence of poliomyelitis and many without a history of any other febrile illness, while under the periodic observation of the investigators during non-epidemic years Using 200 LD_{50} of virus in tests on mice, they found titres of 1 2,048 in 75%, 1 . 512 in 4%, 1 128 in 8%, 1 32 in 8%, and 1 8 in 4% More recently, Melnick & Ledinko[36] had an opportunity to correlate tests for all three types of poliomyelitis antibody on sera obtained from children both before and after an epidemic of poliomyelitis caused by type 1 virus in Winston-Salem, North Carolina, USA There were no infections from type 3 virus Among 35 children who developed type 1 antibody without any reportable illness during the epidemic period, 88% had titres of from 1 100 to 1 . 1,000 against 100 tissue-culture doses of virus, and the remainder had titres of 1 10 Among 41 children who developed type 2 antibody without any reportable disease during this period, 49% had titres of 1 100 or more, 10% had titres of over 1 10 but less than 1 100, and 41% had titres of 1 10 or less Although some of these very low titres of type 2 antibody might represent a transitory group-response to infection with type 1 virus,[50] this cannot be the explanation in all instances, since some of the low titres developed in the absence of type 1 antibody.

serum as early as 12 hours after onset of first symptoms and before appearance of paralysis,[62] and then continued to increase in titre over a period of several weeks The observation of Steigman & Sabin [62] that, in tests with undiluted sera against varying amounts of virus, the acute-phase as well as the convalescent-phase sera often neutralized certain maximum amounts of the patient's own virus, explains some of the incomprehensible results of earlier years when this method was commonly used. It is only when varying dilutions of serum were tested against an appropriate constant amount of virus that it became possible to demonstrate the classical pattern of specific-antibody rise during convalescence. Gener-

developed type 2 antibody between one and three months after onset of their clinical illness, which was due to another type of virus [62] Because of the

in titre during the first two to four weeks after onset, and then either completely disappeared or dropped in titre by three months after onset, while

type 1 and type 2 poliomyelitis viruses. The existence of an antigenic relationship between all three types of poliomyelitis virus is even more apparent in the development of complement-fixing antibody for the heterotypic as well as the homotypic types of virus by a large proportion of patients [13, 63]

Only one study has been reported thus far on the persistence of antibody against the infecting strain of virus recovered from the patients during the acute phase of illness.[68] Serum dilution titres of 1 180 to at least 1 · 1,024 were found in a group of patients with the paralytic disease, and there was no evidence of a significant change in titre between three months and three years after onset. Although tissue cultures have been used extensively during the past year or two for measurement of antibody, there is, as yet, no report of a systematic study by this more refined technique of the development and persistence of homotypic and heterotypic neutralizing antibodies in patients with paralytic or non-paralytic forms of infection caused by the three types of virus. Since there are indications of antigenic variation among strains of the same immunological type

While not all animals whose sera have been found to neutralize poliomyelitis virus have as yet been thoroughly investigated, the studies in my laboratory during the past two years have elucidated the situation in cattle. Bovine colostrum almost invariably neutralized type 2 poliomyelitis virus, and the serum of from 75% to 90% of cattle over three years of age neutralized not only type 2 poliomyelitis virus, but also type 1, and, in a lower incidence, type 3 In calves of between four and six months of age, the virus was rarely neutralized The neutralizing substances, with only rare exceptions, were present in very low titre, but otherwise possessed all the properties exhibited by the antibody in human serum, *including predominant association with the gamma globulin fraction* [52] However, calves devoid of neutralizing antibody could not be infected by a virulent strain of poliomyelitis virus by either oral, intramuscular, or intracerebral administration, and failed to develop antibody to it It was concluded, therefore, that in cattle, at least, the antibody appearing in low titre with advancing age was probably the result of infection with *another agent possessing antigenic groups* that are related to those of poliomyelitis virus

Incidence of Different Types of Poliomyelitis Antibody in Different Circumstances

The unexpectedly high incidence of paralytic poliomyelitis during the second World War among the military personnel of western nations stationed in countries with lower standards of hygiene strongly emphasized the point that immunity to poliomyelitis was not acquired simply by growing older [46] It was particularly important to realize this because it had been demonstrated with a number of other neurotropic viruses that many experimental animals acquired a " maturation resistance ", not to infection, but to invasion of the central nervous system (CNS) or progression of the virus within it [46] Since the native populations among whom the military personnel lived were either seemingly free of clinical manifestations of poliomyelitis or had only sporadic cases in early infancy, it became of interest to use serological methods as a measure of the extent of viral dissemination at different periods of life in different countries

and Japan [43, 49] Other investigators, notably Hammon [24] and Paul [42] and their associates, have carried out similar *comparative serological surveys* in other parts of the world I have brought together some of the reported data in table I by recalculating the incidence for several comparable age-groups It should be stressed here that the data for American cities were

These observations on antibody development, taken together with many others on isolation of virus from children without signs or symptoms of disease,[21] establish that clinically inapparent infection can occur. It is also evident that, while the majority of inapparent infections give rise to as high titres of antibody as clinically recognized infections, there is a variable incidence of low titres In this connexion it may be mentioned that I have observed that cynomolgus monkeys which develop inapparent infection after oral administration of large doses of virulent virus generally exhibit antibody titres of from 1 . 100 to 1 : 1,000, while inapparent infections resulting from repeated ingestion of minute doses of virulent virus or of large doses of essentially " avirulent " strains produce a varying proportion of titres of 1 25 or less.

Antibodies as an index to previous infection

It was demonstrated many years ago in limited tests in monkeys that the sera of human adults with no history of the disease, from parts of the world where poliomyelitis occurred in epidemic form, as well as from other parts where it was practically unknown, almost invariably neutralized the virus There was a long period, however, when it was doubted that the neutralizing capacity was due to antibody, or that it resulted from infection with poliomyelitis virus. Even after the mouse became available for large-scale tests with type 2 poliomyelitis virus, and it became thoroughly established that the neutralizing factor was transmitted by way of the placenta and, like other specific antibodies resulting from infection, then disappeared in early infancy, subsequently reappearing at different rates with advancing age, there was still the difficulty that the sera of a variety of animals presumably insusceptible to poliomyelitis also neutralized varying amounts of the virus Among the many observations which gradually served to dispel the doubts that the presence of neutralizing antibody in human serum can be taken as an index to previous infection with poliomyelitis virus, the following may be mentioned ·

(*a*) demonstration by quantitative methods with infecting or homotypic strains of virus that the antibody response in human poliomyelitis is not only similar to that occurring in other virus infections, but that the level of antibody is generally high;

(*b*) demonstration by Gear and his associates [21] that the acquisition of antibody by African natives during early infancy in the absence of clinical manifestations of poliomyelitis is associated with a high incidence of infection as measured by recovery of virus from the stools;

(*c*) demonstration that the antibodies do not appear as a result of maturation in the absence of the virus, as reflected in tests on sera of Eskimoes of different ages,[43] or of individuals of different socio-economic status residing in the same community [24, 36, 49]

obtained predominantly on individuals of the lower-income groups, and that there is now available enough statistically significant information to indicate that in the higher-income groups antibody is acquired at a very much slower rate [21, 36, 49]. Nevertheless, it is quite clear that among populations with low standards of hygiene as well as great crowding, whether they be Koreans, Okinawans, Japanese, Egyptians, Cubans, or Latin-Americans living in Texas, antibody to type 2 poliomyelitis virus is acquired more extensively and at a very much earlier age. The illuminating data of Hammon and his associates [24] on certain parts of California, Texas, Mexico, Japan, Guam, and other Pacific Islands, were not included in table 1 because they could not be fitted into comparable age-groupings, but they show the same phenomenon. Furthermore, they show the importance of the economic status on the rate at which antibody is acquired, an observation which has been fully confirmed in a number of other studies. The primitive sanitary conditions obtaining among the isolated Eskimoes in north Alaska [43] do not begin to play their role until poliomyelitis virus is introduced in the community, and then they help to disseminate it rapidly. Because of the small size of the population and their former isolation, the virus then disappears from the community until it is again introduced years later. The most plausible interpretation of the results obtained by Paul et al. [43] for all three types of poliomyelitis antibody in this Eskimo community is that type 3 was imported about 1905, type 1 about 1915, and type 2 in 1930, all disseminating extensively for a short time and then disappearing.

Although extensive testing for antibody against types 1 and 3 poliomyelitis virus has become possible only since the recent advent of tissue-culture methods,[18, 45] the studies on sera from Cairo (Egypt),[41] Winston-Salem, N.C., USA,[36] Pittsburgh, Pa., USA,[49] and French Morocco (D. M. Horstmann, personal communication) indicate that the same principles obtain. Salk's data for the vicinity of Pittsburgh indicated that 60% of the children between three and eight years of age possessed no antibody for any of the three types, and while the incidence of the different types of antibody increased at different rates with advancing years, somewhat more than 50% of 53 people aged 18 years or over still lacked antibody for one or another type. The important type 1 antibodies built up irregularly from an incidence of about 5% at between three and five years of age to about 40% at 15-17 years, and reached approximately 80% in the group aged 18 years and over. The very illuminating studies of Melnick & Ledinko [36] in Winston-Salem, N.C., USA, suggest that fairly high infection-rates with type 2 poliomyelitis may be a yearly event, while the type 1 and type 3 viruses may exhibit very low or negligible infection-rates except during certain epidemic years. Moreover, it is of interest that during the single epidemic season of their study the *infection*-rate for type 1 virus

TABLE I. INCIDENCE OF NEUTRALIZING ANTIBODY FOR TYPE 2 POLIOMYELITIS VIRUS AT DIFFERENT AGES IN DIFFERENT PARTS OF THE WORLD

City or country	Year sera collected	Percentage positive at indicated age					Number of sera tested at indicated age					Source of data
		2–3	4	5–9	10–14	15 +	2 + 3	4	5–9	10–14	15 +	
Baltimore, USA	1941–2 1947–8	22	49	72	84	89	180	45	148	142	92	Turner et al [45]
Cincinnati, USA	1947	20	40 *	43	43	100 **	40	40 *	63	44	30	Sabin [40]
Winston-Salem, N C, USA; pre-epidemic	1948	17	22			90	46	16			19	Melnick & Ledinko [38]
Japan	1946	50	64 *	89	93	90	55	67 *	37	27	40	Sabin [40]
Korea and Okinawa	1946	70	97 *			100	36	31 *			30	Sabin [40]
Cairo, Egypt	1950	79	100			96	53	16			49	Paul et al [41]
		1–4					1–4					
Texas, USA (Latin-American)	1948	56		84	94	95	65		49	31	40	Paul et al [43]
Miami, Fla, USA	1950	10		50	71	80	10		18	24	162	Paul et al [43]
Havana, Cuba	1950	64		75	73	66	22		16	15	29	Paul et al [43]
Munich, Germany	1951	20		50	47	74	25		22	15	31	Paul et al [43]
Iceland	1950	29		49	41	75	14		33	31	110	Paul et al [43]
Alaska	1949	0		4	0	15–19: 10 20 +: 83	5		49	45	15–19: 30 20 +: 114	Paul et al [43]
French Morocco	1953	60		88	93	91	62		41	40	32	Horstmann (personal communication)

* These data are for ages 4 and 5

** This applies to people aged 18–50 from a lower-income group, while only 50% were positive among people of similar age from a middle-income group

TABLE II. TITRES OF NEUTRALIZING ANTIBODY FOR TYPE 2 POLIOMYELITIS VIRUS IN CHILDREN AFTER RECENT INAPPARENT INFECTION, AND IN OLDER NORMAL POPULATIONS

Group of normal individuals aged	Number studied	LD_{50} virus used in test	Percentage of sera exhibiting indicated serum-dilution titre					Source of data
			1,000 +	500 to < 1,000	100 to < 500	> 10 to < 100	10 or less	
Under 15 years	24	200	75	4	8	8	4	Turner et al [65]
(Few months after inapparent infection)	41	100		49		10	41	Melnick & Ledinko [34]
14 to 75 years	51	32	4	18	8	53	18	Bell [1]
17 to 37 years	22	50		5	23	64	9	Sabin
19 to 72 years (Eskimoes)	27	80		.	52	.	48	Paul et al [43]

fact that 52% of the Eskimoes tested by Paul et al [43] 19 years after the last presumable exposure to infection with type 2 virus still had titres of 1 · 100 indicates not only that antibody can persist without re-infection but that it can do so in high titre The Alaskan data for type 1 and type 3 antibodies indicate persistence for more than 30 or 40 years The direct studies with the patients' own infecting strains of type 1 virus reported by Winsser & Sabin [68] showed no significant drop in titre in simultaneous tests on sera obtained three months and three years after onset in a group of patients who lived under conditions which did not indicate widespread dissemination of virus.

It has been suggested, however, that the only plausible explanation for maintenance of high infection-rates in early childhood among population groups inhabiting semi-isolated islands, such as Guam, is that re-infection of immune adults helps to maintain the infectious cycle (Hammon, 1949 [22]) While there is, as yet, no direct evidence for this assumption, there are some indirect data which seem to support it, while other data suggest that re-infection of immune adults may occur only infrequently. Foremost among the supporting data is the finding that poliomyelitis virus has been recovered from a considerable number of adult familial associates or other intimate contacts of clinical cases of poliomyelitis. In a summary, based on more than 25 reports of different investigators between 1939 and 1951, G C Brown (personal communication) found that virus was recovered from 21% of 115 adult familial associates, as compared with 54% of positive isolations from 195 children in the same groups On the assumption that the incidence of immunes among adults is more

was 45% (of those without antibody before the epidemic) among children of the lower socio-economic groups, and only 7% in the upper socio-economic groups, while for type 2 virus it was 26 and 14 respectively for the two groups D M Horstmann's recent data (personal communication) on French Morocco indicate, however, that in another region with a different way of life high infection-rates for all three types of poliomyelitis virus can occur in the absence of epidemics, the incidence of all three types of antibody being approximately 75% in children of from two to four years of age.

Significance of High and Low Titres of Antibody in Normal Population, and their Relation to Re-infection and Resistance to Paralysis

It has already been pointed out that clinically inapparent infections with both type 1 and type 2 poliomyelitis viruses have been found to produce fairly high titres of neutralizing antibody in the majority of children. And yet, as may be seen in table II, among young adults and older people a fairly high proportion have been found to possess lower titres of type 2 antibody The issue here is whether poliomyelitis antibody, once acquired, persists for many years, and even for a lifetime, or whether the observed variations in titre mean that antibody is gradually lost unless it is boosted by repeated infections Before an analysis of this problem is attempted, it must be realized that, until studies are carried out with a number of different strains of the same immunological type, one cannot be certain that some of the low titres may not be converted to high ones in tests with other strains For example, studies (unpublished) carried out in my laboratory in collaboration with A. H Fieldsteel have shown that some cynomolgus monkeys which develop type 2 neutralizing antibody after ingestion of the Y-SK strain may exhibit very high titres in tests with the homotypic Lansing strain but very low titres in tests with similar amounts of the MEF_1 strain However, both dosage and the virulence of the infecting strain have been found to influence the proportion of monkeys which develop low titres of antibody after inapparent infection In this connexion it is noteworthy that Turner and his associates [65] found only 4% of children in Baltimore with titres of 1 : 10 or less, while Melnick & Ledinko [38] found 41% with such titres among children in Winston-Salem shortly after inapparent infections with type 2 virus. In the same year in Winston-Salem, when type 1 virus was causing an epidemic, 88% of the children inapparently infected with this type exhibited titres of 1 : 100 or more.

While it is, of course, conceivable that titres of poliomyelitis antibody may diminish over the years, there are certain indications that they may persist at high levels for many years in the absence of re-infection. The

re-infection may be possible in animals (and perhaps also in human beings) with a low-grade immune response to the original infection Koprowski, Jervis & Norton[29] observed a few such limited re-infections in tests on human beings Bodian's demonstration[6] that high titres of passively administered antibody neither prevent alimentary infection nor affect the extent of virus excretion in chimpanzees indicates that a local "tissue immunity" to re-infection exists in animals subclinically infected by the oral route which is not a function of the circulating antibody It is of interest that the two chimpanzees in Bodian's experiment, which had polio-myelitis antibody as a result of spontaneous infection, failed to excrete virus in the stools even though one of them with an antibody titre of 1 25 showed a fourfold rise in antibody after ingestion of homotypic virus. In recent tests on three human adults I found that re-infection may occur after ingestion of 10^6 to 10^7 TCD_{50} of "avirulent" viruses when the level of spontaneously acquired antibody is low One of the volunteers, with an initial serum dilution titre of 1 15 against type 3 virus, excreted 10^2 TCD_{50} of type 3 virus per gram of faeces on the seventh day, but not thereafter, and his antibody titre increased to 1 320, while another volunteer, with an initial serum dilution titre of 1 32, did not excrete virus and exhibited no rise in antibody The third volunteer, with an initial serum dilution titre of 1 32 against type 2 virus, excreted approximately 10^3 TCD_{50} of virus per gram of faeces seven and ten days after ingestion of 10^6 TCD_{50} of "avirulent" type 2 virus, but not thereafter, and his antibody titre rose to 1 3,200 While further work on the carrier status of immune adults is highly desirable, the existing data strongly suggest that inapparent infection produces long-lasting immunity to paralysis, and that re-infection with homotypic viruses, associated with a transitory and low level of virus excretion, may occur in individuals with low levels of antibody

Paradox of Negligible or Low Incidence of Paralysis in Association with Widespread Infection in Early Childhood

While there is much uncertainty regarding the actual incidence of paralytic poliomyelitis in certain parts of the world, there seems to be little doubt now that, among the natives of many parts of Africa, Asia, the Philippines, Guam, and other regions where dissemination of the virus is so extensive that 80% or more of children acquire antibodies by the time they are between three and four years old, the disease rarely, if ever, occurs among adults, and its incidence is negligible or very low even in early childhood Since the unexpectedly high incidence of paralytic polio-myelitis among foreign troops or other peoples living in their midst indicates that virulent strains of virus are present in those regions, it has been

than 2·5 times that among children, the above results have been interpreted as indicating re-infection among immune adults It is not improbable, however, that in the American communities and selected households in which these tests were performed, 50% of the adults may have been without antibodies for the type of virus they carried (see reference to Salk's data[59] on page 305) In a similar study on 12 families in South Africa, J. H S. Gear (personal communication) made the important observation that, while virus was frequently recovered from the European familial associates, none was obtained from any of the African servants; judging from Gear's other observations there is a very high probability that the Africans were immune. Furthermore, in a study involving tests for neutralizing antibodies, as well as presence of virus in stools, as an indication of subclinical infection among members of three families with a diagnosed case of poliomyelitis, Brown & Ainslie[9] found virus in only one out of nine associates aged 15 years or over, but in all six of those aged 10 years or less The older group all had antibody for the Lansing virus as well as for the heterotypic "family virus" (the one adult carrier was developing antibody for the "family virus" at the time of test, as evidenced by a rising titre), while none of the younger group had antibodies for Lansing virus at the time the first stool specimen was tested. G C. Brown (personal communication) has obtained similar results in further studies on additional families These data throw considerable doubt on the hypothesis that immune adults can be re-infected and thus contribute to the dissemination of virus in a community exhibiting evidence of almost continuous widespread infection In line with these data in human beings are the observations of Melnick & Horstmann,[34] Horstmann & Melnick,[26] and Howe, Bodian & Morgan[28] on re-infection in chimpanzees subclinically infected by the oral route Using homotypic strains of virus, the former investigators found one re-infection in 12 chimpanzees, and the latter observed four re-infections in 22 challenges, two of these re-infections are of a dubious nature since virus was recovered only six days after inoculation and might have represented some of the ingested material. It would appear that probably less than 10% of immune animals can be re-infected with homotypic viruses, and the duration of virus excretion (and perhaps also the quantity of virus excreted) is less than in control chimpanzees or in chimpanzees challenged with heterotypic viruses. I have observed that cynomolgus monkeys which develop serum-dilution antibody titres of 1 25 or less, as a result either of repeated ingestion of minute amounts of virulent virus or of large amounts of "avirulent" virus, show a fourfold or greater rise in antibody after they are fed large amounts of the same strain of virulent virus, while no such rise in antibody occurs in monkeys which exhibit higher titres of antibody as a result of the original infection. This would suggest that limited

occurred after the first 12 months of life. Thus in the studies of Paul and his associates in Egypt,[41] 7% had type 2 antibodies at between 7 and 12 months of age, while 57% were positive between one and two years of age While the incidence of type 1 and type 3 antibodies in the 7- to 12-month age-group was higher than that of type 2, the total proportion infected was still rather low It is of interest that in Horstmann's recent study on sera from French Morocco (personal communication), utilizing tissue-culture techniques, the incidence of all three types of antibody was 33%-38% among native infants between 4 and 12 months of age A breakdown of the incidence of positive sera, occurring in the 4- to 5-month, 7- to 9-month, 10- to 12-month, and 13- to 23-month age-groups, did not show significant differences, while in the age-group of 2-4 years the

The serological data on infants of different ages referred to above also have a bearing on the possible role of breast-feeding as a factor which might play a part after the maternally transmitted antibody has disappeared from the circulation By the third month of life breast-fed infants daily consume as much as 1,000 ml of milk, and it was conceivable that if the milk contained antipoliomyelitic substances it might exert an effect in the alimentary tract where it is believed the virus has to establish itself Tests performed in my laboratory[49] on the milk of 40 Cincinnati mothers indicated that antipoliomyelitic substances were present in the milk of all those whose serum also neutralized poliomyelitis virus Among 30 mothers from the lower-income groups, all had antibody in their serum and all of the 10 milks collected between two and five days after delivery, as well as 75% of those collected between 38 and 340 days after delivery, neutralized poliomyelitis virus Among 10 mothers from a higher-income group five had no antibody in their serum, and six of the milks obtained within five days after delivery were completely devoid of activity The antipoliomyelitic factor in human milk was found to have the same properties as antibody in the serum Its properties were quite distinct from other antiviral factors which were found in human milk, without reference to the presence of antibodies in the serum, or previous exposure to infection (unpublished data of A B Sabin and A H Fieldsteel) Experiments were carried out in cynomolgus monkeys to determine the effect of drinking antipoliomyelitic milk on infection with poliomyelitis virus by the oral route The human milk was made up of specimens collected between two and five days after delivery, which were found to contain the highest concentration of antibody, i e, on the average a 1 : 20 dilution protected

difficult to understand why the incidence of paralysis is low or negligible among the indigenous children I should like to discuss three hypotheses which, separately or together, have at one time or another been considered in explanation of this paradox (1) inapparent infection under cover of placentally transmitted maternal antibody, (2) protective effect of breast-feeding continued beyond the first six months of life; and (3) the relative mildness of the infection in early childhood and its greater severity in older age-groups

Tests by many investigators have established that poliomyelitis antibodies follow the patterns of other antibodies in human beings with regard to their transmission across the placenta and the period of their persistence during the first months of postnatal life [65, 36, 42] The placentally transmitted antibody is known to diminish at a regular rate, and the persistence is influenced by the original titre. The majority of infants are devoid of placentally transmitted antibodies at between five and six months It had occurred to many people that, where poliomyelitis viruses are being extensively disseminated, infants might acquire inapparent infections while under the protection of the placentally transmitted antibody It seemed to me that if the postulated events actually occurred on a very large scale, the incidence of poliomyelitis antibody between the sixth and twelfth months of life should be high in parts of the world where the viruses were being disseminated very extensively and rapidly, in contrast to the very low incidence observed in the USA in age-groups under two years, even among children from very-low-income groups Accordingly, early in 1947 I undertook to compare the incidence of Lansing antibodies, particularly in the age-group of 9-23 months, among the children of the lower-income groups in one American city (Cincinnati), one German city (Berlin), and those in Korea, Okinawa, Japan, and China In this particular study it was found that, while only 2% of 43 children in this age-group in Cincinnati had antibodies, the incidence was 13% among 23 from Korea and Okinawa, and 23% among 47 from Japan [49] Tests for type 2 antibody on the sera of children from Berlin, Germany, at the end of the serious epidemic of 1947 showed only 8% positive among 12 aged 9-11 months, and 13% positive among 22 aged 12-23 months. Similar tests on 14 sera from children in China aged between 9 months and 2 years yielded approximately 40% positives. It was evident, therefore, that while the incidence was somewhat higher in the Far East the proportion of infants who acquire antibody, while they might have been protected by the placentally transmitted immunity, is small and could not account for the negligible or very low incidence of the paralytic disease in early childhood in those countries. The precise age at which the most rapid acquisition occurs varies in different population groups, but all studies in which tests were made on 7- to 12-month age-groups indicated that the rapid rise in antibody

period is not sufficiently different to account for the paradox here under discussion.

Since the factors just discussed cannot by themselves account for the association of low incidence of paralysis with widespread infection in early childhood, it becomes necessary to consider other factors, among which virulence of different strains of virus as well as dosage deserves special attention I have discussed elsewhere some of the epidemiological evidence indicating that widespread immunity might be acquired from infection with strains of low virulence.[49] A good example may be found in the situation which obtained in Malta before the serious epidemic which began in 1942[61] The available records for the preceding 40 years indicated an incidence of recognized poliomyelitis which did not exceed 2 per 100,000 per year Yet, when the epidemic occurred in 1942, instead of producing paralysis indiscriminately in people of various ages, it was limited to those under five years of age in the Maltese population However, British troops who were on the island at that time succumbed with paralysis at a rate which was similar to that obtaining for the Maltese children under five, while the Maltese troops and other older Maltese residents remained essentially unaffected This experience strongly suggests that when a highly virulent strain finds enough susceptible children under five years of age it extracts that high toll in paralysis which gives rise to an epidemic of poliomyelitis with an infantile pattern It is also obvious that during the preceding 40 years the Maltese children must have become immunized without having to pay this high toll in paralysis If we assume that in regions with underdeveloped sanitation and hygiene, as well as a certain amount of isolation from the extensive traffic in the world at large, there are being disseminated predominantly strains of poliomyelitis virus of low virulence, we can understand how the introduction of a virulent strain in such a community might ordinarily find too much competition and too few susceptible individuals to produce more than a few recognized cases of the disease in the indigenous population That such virulent strains are periodically present in such areas is evident from the relatively high incidence observed among troops and other foreigners who may be living in close association with the local population Before the advent of tissue-culture methods it was possible to recover only strains of moderate or high virulence because the criterion of isolation was the production of paralysis in monkeys It should now become possible to test the hypothesis of a high prevalence of avirulent or low-virulent strains, particularly in those areas of the world where immunity is extensively acquired at a very early age Similar studies can, of course, also be carried out on healthy children during non-epidemic periods in other countries, and such a study is now in progress in my laboratory Tests recently completed by M Ramon Alvarez and myself on rectal swabs from 1,566 healthy Cincinnati children, who had no

against 50 LD_{50} of virus The human milk was in each instance administered by mouth, 20 ml three times a day, for one day before the virus, during the three days of virus administration, and for three days thereafter. No beneficial effect was observed, since 50% of the 24 cynomolgus monkeys used in the test developed paralytic poliomyelitis—a paralytic-rate which was almost the same as in the controls The fact that breast-feeding is continued for two years or longer in some population groups had been thought by some to contribute to the phenomenon of the association of a high incidence of immunity in early childhood with a negligible incidence of the paralytic disease in certain parts of the world. However, the serological data just quoted, which indicated that in the Far East and in certain other countries from 60% to 85% of the children are still without poliomyelitis antibody by the time breast-feeding is discontinued, as well as the negative results obtained in the experimental studies in cynomolgus monkeys, make it quite clear that breast-feeding by itself cannot account for the paradox here under consideration

This brings us to an analysis of the third hypothesis, namely, that the mildness of poliomyelitis infection acquired during the first four years of life might account for the negligible or low incidence of paralysis. In my opinion, this hypothesis is untenable for the following reasons

(1) The earliest epidemics of poliomyelitis, as well as many of those still occurring in certain parts of the world, are characterized by the typical infantile pattern, in which children of one, two, three, and even four years of age are predominantly attacked. It cannot be said, therefore, that children of this age have a sufficiently high resistance to the paralytic consequences of poliomyelitis infection to account for the low incidence observed in the areas where antibodies are acquired predominantly during the period of between one and four years of age.

(2) While it is true that paralysis occurring in young children is generally less severe than that which occurs in the higher age-groups, and while it is true that the incidence of non-paralytic poliomyelitis has been observed to

acquired at a very early age. In the first truly quantitative study of this type carried out before and after an epidemic caused by type I poliomyelitis virus in Winston-Salem, Melnick & Ledinko [26] calculated that the number of clinically recognized cases per thousand subclinical infections was 10 for the 1- to 2-year age-group, 14 for the 3- to 4-year age-group, 16 for the 5- to 9-year age-group, and 11 for the 10- to 14-year age-group. This provides actual evidence that the paralytic attack-rate in nonimmune children in the range of 1-14 years of age during an epidemic

IMMUNITY IN EXPERIMENTAL ANIMALS

Development of Antibody in Experimentally Infected Monkeys and Chimpanzees

The most important fact about development of antibody in experimentally infected animals is that, after infection by the intracerebral or intranasal routes, antibody as a rule develops very slowly, sometimes weeks after onset of paralysis,[54] while after infection by the oral route antibody is formed rapidly[32] and is usually present by the time paralysis is first observed, even when such paralysis occurs as early as between seven and nine days after the first dose of virus The development of antibody after oral administration of the virus is a function, not of the concentration of virus ingested, as measured by intracerebral titre of the material, but rather of the capacity of the virus to produce infection by way of the alimentary tract[33 67] Some strains are almost completely devoid of the property to infect and produce antibody by the oral route in cynomolgus monkeys Rhesus monkeys are much more difficult to infect by mouth than cynomolgus monkeys, and cynomolgus monkeys more difficult than chimpanzees The titres of antibody measured by the serum-dilution technique against 32 to 100 infective doses of virus, either in mice or in tissue cultures, generally reach levels of 1 100 to 1 1,000 and sometimes higher Titres of this magnitude have been observed both for type 1 antibody in cynomolgus monkeys infected with the Mahoney strain and for type 2 antibody in monkeys infected with the Y-SK strain, also in many cynomolgus monkeys which exhibited no lesions in large numbers of sections from the nervous system It is of interest that cynomolgus monkeys which develop antibody after repeated ingestion of minute doses of Y-SK virus over a period of 90 days frequently (about 50%) exhibited very low titres in the range of 1 2 to 1 25

Chimpanzees infected with poliomyelitis virus by the oral route develop antibodies as rapidly and in as high titre as was observed in cynomolgus monkeys There is evidence, however, that strains of poliomyelitis virus which are incapable of producing antibodies after oral administration to cynomolgus monkeys can do so when they are fed to chimpanzees Thus Melnick[33] reported that Lansing virus fed to cynomolgus monkeys failed to produce antibody, and we have confirmed it in a test on 14 monkeys which were fed Lansing virus that had been submitted to two intracerebral passages in cynomolgus monkeys Howe and his associates,[28] however, had little difficulty in demonstrating antibody development in chimpanzees which received the Lansing virus, although this strain apparently did not multiply very extensively in the alimentary tract of these animals In

known contact with recognized cases of poliomyelitis, yielded five strains of poliomyelitis virus (three type 2 and two type 3), all of which were avirulent for monkeys by the intracerebral route.

Another factor to be considered is that small doses of virus may give rise to a higher rate of inapparent infection than large doses. In a hyperendemic region the conditions of poor sanitation and hygiene are conducive to dissemination of virus not only by intimate personal association, but also by flies, cockroaches, and perhaps even water Ward's demonstration[66] (and from personal communication) of poliomyelitis virus in five of 36 lots of Musca flies trapped at random in Cairo and surrounding villages without reference to any index cases of poliomyelitis shows how easy it must be to come in contact with small amounts of virus in such an environment. It is also conceivable that small amounts of virus introduced through abrasions in the skin of infants might play a role, as well as ingestion of the virus The role of dosage was investigated in my laboratory by feeding experiments in cynomolgus monkeys, but different results were obtained with two strains With the Y-SK (type 2) strain it was found that, as the amount of virus ingested diminished, the proportion of inapparent infections increased By the daily administration of highly diluted virus over a period of 90 days it was possible to obtain at least nine inapparent infections (as judged by the development of antibody) for each paralytic infection, as compared to a ratio of 1 1 when a large amount of virus was fed over a period of a few days It was furthermore of interest that even those monkeys which failed to develop demonstrable antibody after the longer period of feeding of minute doses of virus showed a statistically significant resistance to the paralytic consequences of infection when they were challenged by a large dose of the same virus given by mouth[56] How many strains occurring in nature may behave like the Y-SK virus in cynomolgus monkeys is not known When tests were performed with the type 1 Mahoney strain, dosage appeared to have no effect on the proportion of inapparent infections, regardless of the dose ingested, there were roughly two paralytic infections for each inapparent infection[53] However, as will be described later, when an avirulent variant was produced experimentally from this Mahoney strain it proved capable, after oral administration, of causing inapparent infections in cynomolgus monkeys without any ...ted paralytic infections[53]. It is not at all unlikely that future obser-

avirulent or of low virulence.

that in the inapparently infected cynomolgus monkeys there was no correlation between the level of antibodies in the serum and the resistance to intracerebral or intranasal challenge This is in contrast to the results reported by Morgan [40] who found that after intramuscular injection of living Lansing virus in rhesus monkeys there was no regular resistance to intracerebral challenge until the level of circulating antibody had been raised to a titre of about 1 1,000 It is of interest that during the course of the typing programme [14 15] it was found that rhesus monkeys injected intramuscularly with the Brunhilde virus became resistant to intracerebral challenge before such high levels of neutralizing antibody were achieved All this points to a difference between the immunity which follows inapparent infection and that which is merely a consequence of antibody engendered by preformed antigen

Only a limited number of studies have been made thus far on active immunity to challenge by the oral route, especially in animals which were initially infected by the same route It has already been mentioned that Melnick & Horstmann,[24] Horstmann & Melnick,[26] and Howe, Bodian & Morgan [28] had shown that chimpanzees, as a rule, are resistant to both re-infection and paralysis when they are fed homotypic virus a second time It was pointed out that while perhaps 10% of the chimpanzees again became carriers of the homotypic virus there were indications that the carrier-state did not persist for very long In contrast to this it was found that after feeding of heterotypic virus the incidence of the carrier-state was as high as among the controls The only data on immunity to paralysis after re-infection of chimpanzees with heterotypic virus is contained in the experiments of Howe, Bodian & Morgan [28] who found that chimpanzees that had been previously infected with Lansing virus (type 2) exhibited the same incidence of paralysis (25%) when they were subsequently fed Brunhilde virus (type 1) as did chimpanzees which were fed the Brunhilde virus for the first time It should be remembered, however, that this lack of cross-immunity to paralysis between heterotypic viruses may not be the same for all strains For example, in an experiment which I performed in association with Winsser it was found that the incidence of paralysis among 24 cynomolgus monkeys, which had previously experienced inapparent infection after ingestion of Y-SK virus, was significantly less (33%) after ingestion of virulent type 1 Mahoney virus than in 20 controls simultaneously fed the same virus (60%) Further evidence that the previous infection with Y-SK virus had modified the response to subsequent infection with the Mahoney virus was obtained in the reversal of the ratio of paralytic to inapparent infection in the two groups Thus, in the control group there were 12 paralytic infections to six inapparent infections, while among the 24 monkeys which had been previously infected with the Y-SK virus the ratio was just the reverse, in that there were

chimpanzees, antibody development after ingestion of virus is associated with a period of virus excretion in the faeces, although this may occasionally be so brief or so limited that virus is not detected [26, 28]

Resistance to re-infection

It has been shown that monkeys which are paralysed as a result of intracerebral or intranasal infection are resistant to challenge with the same strain of virus by the intracerebral or intranasal routes at a time *when antibody cannot be detected in the serum.*[54] *Although it has been* reported that neutralizing substances for the virus could be demonstrated in the nervous tissue at a time when it is absent in the serum of monkeys paralysed by Lansing virus,[39] no such neutralizing substances were found in the nervous system of paralysed monkeys infected with other strains of poliomyelitis virus [54, 55] It would appear at present that there is a certain tissue-resistance in the affected nervous system which is not a function of circulating antibodies That this resistance is specific for poliomyelitis was established by Bodian [2] who showed that paralysed monkeys convalescent from infection with poliomyelitis virus were not resistant to inoculation with the virus of Western equine encephalomyelitis Although a certain number of equivocal reports suggested that some paralysed monkeys may not resist a second injection of the same type, or even strain, of poliomyelitis virus, the results of Bodian's carefully controlled experiments indicate that paralysed monkeys are invariably immune to intracerebral challenge with the same type of poliomyelitis virus [2] Moreover, he found a significant degree of resistance to challenge with heterotypic strains of virus , the paralytic attack-rate was often only half that occurring in the controls, and the degree of involvement in those monkeys that did develop secondary infection as a result of heterotypic virus was invariably less than in the controls This suggests a certain degree of group immunity, which is not reflected in the circulating antibodies which can be detected in such animals The resistance to intracerebral challenge in monkeys which have previously received virus intramuscularly probably varies with the strain of virus that is used for intramuscular injection Strains which readily produce infection by peripheral injection probably give rise to immunity more readily than those which do not produce peripheral infection. This is evident from the fact that in rhesus monkeys it was necessary to give repeated injections of fairly large amounts of live virus before the animals became immune to intracerebral challenge [40] On the other hand, Melnick & Ledinko [35] showed that the majority of cynomolgus monkeys which developed antibodies without paralysis after oral administration of the Y-SK virus were immune to challenge by the intracerebral or intranasal routes. It is of interest also that these investigators found

animal They found not only that these chimpanzees became virus carriers but also that the nervous system was not protected from invasion by the virus These results are not consistent with the subsequent reports by Bodian,[8] who informed me that a re-examination of the histological sections of the chimpanzees in the 1945 experiment has led to considerable doubt that the lesions were of a poliomyelitic nature, except perhaps in the one instance in which there was evidence of invasion by the olfactory pathway.

An important advance was made when Bodian[3] showed that the amount of antibody required to protect monkeys against paralysis following intramuscular injection of virus was very much less than that required to protect them against infection by the intracerebral or intranasal routes This protection was afforded by an amount of human gamma globulin (2 ml per kg) which provided a titre in the circulating blood of 1 25 on the day after injection It is of special interest that Bodian points out that the viruses used in these tests produced initial paralysis predominantly in the inoculated sites, which suggests that the nervous system was being invaded along the regional nerves Bodian[5] subsequently demonstrated that similar amounts of antibody protected cynomolgus monkeys against paralysis resulting from infection by the oral route There has been a tendency to ascribe the protection afforded by these smaller amounts of antibody to the assumption that in the animals infected by the oral route the nervous system is invaded by virus from the blood-stream[4] In my opinion, the localization of paralysis in the intramuscularly inoculated monkeys strongly suggests that in them the virus invaded the nervous system along the regional nerves from the inoculated site in the calf muscles, and that the antibody could have exerted its effect on those peripheral structures in the muscle which have to be infected by the virus before invasion of the nerves can begin Since there is no evidence that more antibody was needed to prevent paralysis after intramuscular than after oral infection, one cannot conclude that the reason relatively small amounts of antibody can protect against paralysis resulting from peripheral inoculation of virus is that it prevents viraemia Just how low a level of antibody is sufficient to protect monkeys against paralysis following oral administration of the virus is not yet clear from available data Bodian[5] has reported only one test on eight monkeys in which the amount of gamma globulin (titre of 1 500 to 1 630) administered was 0 1 ml per kg, giving an estimated barely perceptible amount of antibody in the undiluted serum Although four of the nine controls developed paralysis while the eight treated ones remained without paralysis, this by itself is not a statistically significant result and should not be the basis for statements that barely perceptible amounts of passively introduced antibody can prevent paralysis in orally infected cynomolgus monkeys

16 inapparent infections to eight paralytic infections. Since no antibody for type 1 virus was found in the blood of these monkeys before challenge, there is again a suggestion, as in the experiments on intracerebral challenge,[2] that there may be a degree of cross-immunity between the different immunological types of virus which is not reflected in circulating antibody. It is of interest that infection with the heterotypic virus was not prevented since all the monkeys developed antibody for type 1 virus, but that cross-immunity apparently operated in some way to diminish the incidence of paralysis. The possible existence of a certain degree of cross-immunity between the type 2 Y-SK *strain and the type 1 Mahoney strain received* further support in experiments I carried out in association with Hennessen, which showed that cynomolgus monkeys which received formalinized, completely inactivated Y-SK tissue-culture vaccine exhibited a similar partial resistance to oral challenge with Mahoney virus—22% of 37 vaccinated monkeys were paralysed versus 58% in 59 controls. Here, too, infection was not prevented because the remaining vaccinated monkeys developed type 1 antibody without paralysis Another example of heterotypic cross-immunity is contained in the report of Casals, Olitsky & Brown,[12] who found that a significant proportion of mice vaccinated with formalinized type 2 MEF_1 virus resisted intraspinal challenge with type 3 Leon virus. Observations in my laboratory on the response of cynomolgus monkeys which had been inapparently infected following repeated ingestion of minute doses of Y-SK virus to subsequent challenge with large doses of the same virus indicated not only that they failed to develop paralysis (the incidence in controls was 60%), but also that there was no increase in the level of circulating antibody unless the titre before challenge was less than 1 25. Interestingly enough, one monkey in this experiment with an antibody titre of 1 : 80 before challenge did develop paralysis, but histological examination indicated that the virus had invaded the nervous system by the olfactory pathways

Effect of passively introduced antibody on resistance to paralysis and infection

It has been demonstrated in experiments on both mice and monkeys that when extremely large amounts of antibody are inoculated it is possible to protect a significant proportion of the animals against infection by the intracerebral *or intranasal routes.*[7, 30, 41] *As long as experimental studies* were limited to infections produced by the intracerebral or intranasal routes the impression prevailed that passive immunity could be conferred only by amounts of antibody that were so large that they could not conceivably be used in human beings. As late as 1945 Howe & Bodian[27] reported an unsuccessful prophylactic test on chimpanzees infected by mouth after the administration of 170 ml of hyperimmune serum in each

animal They found not only that these chimpanzees became virus carriers but also that the nervous system was not protected from invasion by the virus. These results are not consistent with the subsequent reports by Bodian,[4] who informed me that a re-examination of the histological sections of the chimpanzees in the 1945 experiment has led to considerable doubt that the lesions were of a poliomyelitic nature, except perhaps in the one instance in which there was evidence of invasion by the olfactory pathway.

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PRESENT STATUS OF WORK ON VACCINATION

Principles and Objectives

The highest paralytic attack-rates in human beings have occurred in certain isolated, also highly inbred, population groups,[49] reaching a maximum of 21% in the 1949 epidemic among Eskimoes of Chesterfield Inlet in the Canadian Arctic. This probably represents the maximum susceptibility to paralysis when human beings of the appropriate genetic constitution are infected for the first time with highly virulent poliomyelitis virus. It is of interest that chimpanzees which are fed large doses of the virulent, type 1 Brunhilde strain exhibit a similar incidence of paralysis.[28] The risk of acquiring paralytic poliomyelitis during the course of one's entire life probably ranges from 1 in 100 to 1 in 100,000, and perhaps even less, in different population groups. It is clear from the preceding summary of our knowledge of immunity to poliomyelitis that the risk does not diminish by the mere process of growing older if there is not an accompanying opportunity for exposure to non-paralysing infections. The main objective of vaccination, therefore, is to remove that 1 in 100 to 1 in 100,000 life-time risk of paralysis by artificially providing long-lasting immunity. The achievement of this objective depends on the outcome of extensive studies of vaccination by means of both killed-virus preparations and living avirulent variants. Such studies have only recently entered their most promising phase as a direct result of the successful utilization of tissue-culture techniques for the propagation and identification of the poliomyelitis viruses, and it should be stressed that the work has only just begun rather than that it is nearly finished. Application of the known principles of inactivation of viruses, together with reliable methods of measuring antigenic potency, are all that is required to determine whether or not the currently available sources of tissue and strains of virus can yield material that is sufficiently potent in practicable dosage to be useful for ultimate large-scale tests of effectiveness in human beings. The greatest advantage of a killed-virus vaccine lies in the possibility of producing preparations that are completely free of paralytogenic properties. The disadvantages are those inherent in all killed-virus vaccines, i.e., the need for large amounts of preformed antigen and for repeated injections, which in the case of poliomyelitis might have to be repeated yearly for the remainder of a person's life, as well as certain potential sensitization reactions after repeated inoculations of foreign protein. The first consideration in live-virus vaccines is safety, and in the case of the poliomyelitis viruses it has only recently become possible experimentally to modify the paralytogenic properties of available strains and to search among healthy children

for naturally occurring "avirulent" viruses The obvious advantage that one might expect from a live-virus vaccine is the possibility of producing long-lasting immunity by a single small dose given by mouth or parenterally, preferably in early infancy while there is the additional protection derived from the placentally transmitted maternal antibodies The need for extensive research on both approaches to the problem is obvious, because it is unwise to predict and assume too much by analogy, and because it might even prove desirable to use a combination of both approaches under certain circumstances.

Animal Experiments with Killed-Virus Vaccine

A very extensive and detailed review of almost all reported experiments on vaccination of animals has recently been published by Boyd[7] The experience of the pre-tissue-culture era can be summarized in the statement that when sufficiently large amounts of inactivated virus were administered in repeated doses over a long period of time it proved possible to immunize a large proportion of monkeys, mice, and cotton-rats to intracerebral inoculation of virus. The cotton-rats and mice appeared to be immunized more readily than the monkeys, but that may only be due to the fact that they received a great deal more antigen per unit of body-weight Comparative quantitative tests in cotton-rats indicated that inactivation by formalin and ultraviolet light yielded material of equivalent antigenic potency The dosages required to protect even a proportion of the animals against intracerebral challenge (in the range of 0 4 g to 1 8 g of virus-containing tissue per pound (0 88 g to 3 9 g per kg) body-weight) were of sufficient magnitude to preclude practical consideration, even if the objection to the use of nerve tissue were to be disregarded No vaccination experiments with challenge by the oral or intramuscular routes are on record, and the quantities of vaccine which might have been effective under these conditions are not known However, experiments in small numbers of chimpanzees and human beings with formalin-inactivated vaccines prepared from the spinal cords of monkeys revealed that even repeated doses did not produce antibody in all individuals, and that antibody for type 1 was more difficult to achieve than for the two other types.

There are, as yet, no detailed reports of experiments on vaccination of animals with poliomyelitis viruses propagated in tissue cultures Enders[18] and Milzer et al[53] briefly mentioned that mice inoculated intraperitoneally with live Lansing virus propagated in tissue culture subsequently resisted intracerebral challenge, and the latter investigators stated that "the degree of such active immunity . was considerably less than that usually achieved by mouse CNS virus". Salk et al[60] in an abstract published in 1952

stated that the antigenicity of formalinized tissue-culture vaccines, as measured by development of antibody in monkeys, was comparable to that obtained with similar vaccines prepared from nervous tissue. This work, however, was done with virus propagated in cultures of monkey testicles, which generally yield lower titres than similar cultures of monkey kidney

Casals et al [12] have reported that a formalinized vaccine prepared from the CNS of suckling mice infected with the specially adapted MEF_1 strain not only protected mice against intracerebral challenge with the homologous MEF_1 (type 2) virus, but also to a significant extent against spinal inoculation of Leon (type 3) virus In my laboratory (in association with W A Hennessen and J. Casals) a comparative study was made of the capacity of this suckling-mouse-brain vaccine and formalinized monkey-kidney tissue-culture vaccines prepared with the MEF_1 and Y-SK strains to protect cynomolgus monkeys against paralysis resulting from oral infection with type 1 (Mahoney) virus All three vaccines happened to have the same high potency ($10^{6.4}$ infective doses per ml) before inactivation, and all were inactivated with 0 4% formalin at about 4°C It is of interest that the homotypic immunogenic activity of the three vaccines was different when tested in mice and monkeys. The suckling-mouse-brain vaccine, after two doses of only 0 01 ml, produced significant resistance to intracerebral challenge in mice, while even three doses of 0 1 ml each, with or without adjuvant, of either of the two tissue-culture vaccines had no demonstrable immunogenic effect against either the homotypic MEF_1 virus or the heterotypic Leon virus In cynomolgus monkeys, on the other hand, the tissue-culture vaccines produced homotypic antibody more readily than the suckling-mouse-brain vaccine. Fourteen days after a single dose of 1 ml (with adjuvant), 90% of 19 monkeys inoculated with tissue-culture vaccine had developed neutralizing antibody, while only 37% of 16 which received the suckling-mouse-brain vaccine did so After three doses, all three vaccines produced homotypic antibody in 100% of the monkeys. The partial protection against paralysis resulting from oral infection with the heterotypic, type 1 Mahoney virus (already mentioned in a previous section on page 318) was obtained with the Y-SK vaccine, but not with the MEF_1 tissue-culture or suckling-mouse-brain vaccines.

A great deal of valuable orienting and quantitative information must still be obtained in work on animals before systematic and reproducible studies can be carried out in human beings For one thing, it is of the utmost importance that a suitable, quantitatively reproducible method of assay be elaborated in readily available small laboratory animals. The experience just cited indicates that tests for active immunity in mice would be most misleading On the other hand, tests for development of antibody in mice, hamsters, cotton-rats, guinea-pigs, or rabbits might lend themselves

most readily to a quantitative measure of antigenic potency. One need hardly caution here against any test in which the sera of a number of animals are pooled; the sera of individual animals inoculated with different amounts of vaccine must be tested separately to permit of calculation of a 50% immunogenic dose. Only after such a method of assay has been elaborated will it be possible to investigate the important practical questions of the best way to inactivate virus, the best strains to use, the optimum methods of storage for retaining the original antigenic potency, and—most important of all—the reproducibility of potency in different lots, and the relationship between antigenic potency obtained by the standard method of assay and the minimal dosage required to produce antibody that will persist for at least six months in almost all persons who have none.

HUMAN TESTS WITH KILLED-VIRUS VACCINES

There are two lessons to be learned from the unfortunate premature tests on about 20,000 children in 1935, which were followed by 12 paralytic cases of poliomyelitis (1) it is unwise to carry out such trials during the poliomyelitis season, and (2) it is unwise to embark on large-scale tests in human beings without adequate information about the product to be tested While no one would disagree with the first lesson, it is obviously much more difficult to obtain agreement on what constitutes adequate information.

Although there are no published data on the properties and behaviour of killed tissue-culture virus vaccines in animals which would give one a standard of reference for evaluation of results obtained in human beings, there are now three published reports of such tests in human beings. Two of these by Salk[58, 59] contain the results of tests with formalinized vaccine and the third by Milzer et al[57] with a vaccine in which the three types of virus were inactivated with ultraviolet light by a special apparatus previously shown to yield good results with poliomyelitis and other viruses The same strains of virus (Mahoney for type 1, MEF_1 for type 2, Saukett for type 3) and monkey-kidney tissue-cultures were used by both In evaluating the results of these tests it is important to bear in mind that one must distinguish between the response of individuals who already have antibody for one or more types and that of individuals who have no antibodies against any of the three types Since it has been shown that human beings who are infected with one type of virus can develop a very transitory neutralizing antibody response to another, and since development of complement-fixing antibody for all three types of virus is very common in human infections, the presence of any one type of antibody may indicate that that individual has, in part at least, been sensitized by antigens common

stated that the antigenicity of formalinized tissue-culture vaccines, as measured by development of antibody in monkeys, was comparable to that obtained with similar vaccines prepared from nervous tissue. This work, however, was done with virus propagated in cultures of monkey testicles, which generally yield lower titres than similar cultures of monkey kidney.

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after vaccination There is no information at present to indicate that this method of ultraviolet irradiation is less suitable for inactivation of poliomyelitis virus than formalin

Only future studies will show whether or not the dose of killed-virus vaccine required for the regular de novo production of antibody, which will persist for at least between six and eight months, is small enough to permit of the practical manufacture of vaccine for millions of individuals from monkey kidneys The ultimate usefulness of such a preparation would also depend on the absence of nephrotoxic effects and of the development of Rh antibodies after repeated injections of the extracts of kidney and rhesus erythrocytes contained in them The report of Freund and his associates[19] that inoculation of extracts of testicle with oily adjuvants and mycobacteria can lead to degeneration of the testicles calls for special caution in repeated injections of other organ and tissue extracts There is no reason to believe, however, that any of the potential difficulties just mentioned cannot be overcome by further technical developments

STUDIES ON "AVIRULENT" VARIANTS OF POLIOMYELITIS VIRUS

The word "avirulent" can hardly be used without many qualifications, which continue to increase with the growth of our knowledge about variation and mutation among the poliomyelitis viruses For practical orientation, however, we can say that a poliomyelitis virus is virulent when it produces paralysis, and avirulent when it does not and is harmless in other respects It may fail to produce paralysis for any of three distinct reasons (1) it may be unable to produce histologically demonstrable damage to the lower motor neurones, or even to multiply in them ; (2) it may produce typical lesions in motor neurones, but be unable to spread sufficiently to affect the large number that need to be destroyed to give rise to clinically apparent paralysis ; (3) it may be unable to reach the motor neurones, not only after peripheral inoculation, but even after intracerebral inoculation Although the last statement may sound peculiar to the uninitiated, a good example of it may be found in the Leon (type 3) and Mahoney (type 1) strains[31] which paralyse mice after spinal, but not after intracerebral, inoculation I have recently segregated similar spinal variants for mice from the Y-SK (type 2) strain, and for cynomolgus monkeys for each of the three types of poliomyelitis virus Virulence or paralytogenic capacity also depends on the host and the route of inoculation Thus, a Brunhilde variant strain which produced lesions and occasional paralysis after intracerebral injection in cynomolgus monkeys produced only antibody without either paralysis or

to all three types of virus. The amount of antigen required for a booster effect can be very small compared to that required for the production of antibody de novo For this reason, preliminary tests for antibody performed with undiluted serum against small doses of virus in the more sensitive kidney tissue-culture media are more valid than those performed with diluted sera in the much less sensitive monkey-testis cultures. While many interesting results of an exploratory nature are contained in Salk's first report, it provided no information on the response of individuals without antibody to the important type 1 antigen The conclusion that "in one series of experiments it appears that antibody for all three immunologic types was induced by the inoculation of small quantities of such vaccines incorporated in a water-in-oil emulsion" is misleading, because for the important type 1 antibody only a booster phenomenon was demonstrated, without formation of antibody de novo The second report [59] contains data showing that nine children possessing no antibody for any of the three types in serum diluted 1 4 exhibited antibody for all three types in dilutions of 1 4 or higher after three doses of vaccine (total of 3 ml) without adjuvant Among six individuals who received only one-third of this amount intracutaneously, all "developed" antibody for types 1 and 3, while two showed none for type 2 The low titres (mostly from 4 to 20) exhibited by these individuals, who appear to have developed antibody de novo, raises the question whether or not the sera would have neutralized strains other than those incorporated in the vaccines, but no information is as yet available on this point The other important question regarding the proportion of individuals who may lose antibody of such low titre after a period of between four and six months also remains unanswered It was stated, however, that the results reported in this last communication "represent the findings obtained with materials that, in terms of methods now available, are obsolete and therefore do not reveal the full potentiality of the application of the principles upon which the present approach is based" [59] The new results are being awaited with interest, but until a standard method of assay is developed it will be most difficult to compare the antigenic potency of different preparations and to determine the minimal dosage required for the regular production of enough antibody in human beings to persist for a minimum of between six and eight months

Milzer et al.[37] inoculated 30 adult volunteers with two doses of ultraviolet-irradiated trivalent vaccine—the first consisting of 0 5 ml mixed with an equal amount of adjuvant, and the second of 1 ml without adjuvant. The same booster phenomena were obtained here, but the amount of antigen was obviously insufficient for the regular production of antibody de novo. Among seven individuals who possessed no type 1 antibody in their undiluted serum before vaccination (it is not clear how many of them possessed antibody for some other type), four failed to develop it

(2) After inoculation of different dilutions in groups of four or five monkeys, neither paralysis nor lesions may be encountered, however, when larger numbers of monkeys are inoculated with the highest concentration of virus, a few may develop paralysis with typical lesions in the spinal cord and a high titre of virus in tissue culture, but negative results on further intracerebral passage in monkeys I have recently been able to show that this phenomenon occurs with strains of virus that are "spinal variants" for the monkey, i e, they will produce generally a very localized type of paralysis and specific lesions after spinal inoculation but not after intracerebral inoculation, except in the occasional instances mentioned above

(3) After intracerebral inoculation of tissue-culture virus of high potency in varying dilutions, a few of those inoculated with the largest amount may develop paralysis with typical lesions in the spinal cord, but no virus can be demonstrated either in tissue culture or by intracerebral passage. However, when spinal-cord suspension from a number of such monkeys is passed intracerebrally, one again encounters an occasional monkey with paralysis and lesions, but without demonstrable virus in tissue culture, and further intracerebral passage from such an animal produces paralysis in all inoculated monkeys However, the virus recovered from them is still devoid of cytopathogenic activity in tissue culture This has been interpreted as the segregation of a new mutant in the monkey brain with a capacity to damage the nervous system but not the epithelial cells or fibroblasts growing out of the monkey's non-nervous tissue in vitro

Data recently accumulated in my laboratory suggest that the mutation-rate of poliomyelitis viruses propagated in monkey kidney tissue-culture is in the range of 1 in 1,000,000 to 1 in 100,000,000 Intracerebral inoculation of monkeys with such large amounts of "intracerebrally avirulent" variants has also brought to light the possible existence of a so-called "sterile mutant" in which typical lesions and paralysis develop without any demonstrable reproduction of infective virus, as well as of a mutant which is virulent by the intracerebral route but not by the subcutaneous

These most recent conclusions are recorded here without the full documentation, which will be published elsewhere, to indicate the problems that are encountered in attempting to answer the question "Is this strain of virus completely avirulent for monkeys?" A strain of virus is obviously not completely avirulent for the monkey when it can still produce paralysis, localized though it may usually be, after being brought directly to the motor neurones During a discussion at the Second International Poliomyelitis Conference Dr S Gard said "Inoculating virus into an experimental animal is like sowing in rocky soil Some seeds fall on the rocks, others in fertile soil" When one has segregated a variant whose activity

lesions in intracerebrally inoculated chimpanzees.[47] This same strain of virus produced antibody in only an occasional cynomolgus monkey after feeding or intramuscular injection in cynomolgus monkeys, but regularly produced antibody in similarly inoculated chimpanzees It is becoming increasingly apparent from such studies that there is a different gradient for paralysis and for inapparent infection among rhesus monkeys, cynomolgus monkeys, and chimpanzees. Thus, the ease with which infection can be produced *by feeding virus (perhaps also by other extraneural routes) increases* in the series of rhesus-cynomolgus-chimpanzee, while the paralytogenic activity is demonstrably less in the chimpanzee than in the monkeys The extensive dissemination of poliomyelitis in human beings suggests that man is as readily, if not more readily, infected than the chimpanzee, while the incidence of paralysis suggests that man is less, rather than more, susceptible The data reported by Turner et al [65] for the natural acquisition of type 2 antibody indicate that thousands can be infected without a single clinically recognized case of poliomyelitis due to this virus Accordingly, experimental tests even on hundreds of children could not by themselves indicate whether or not a given type 2 strain of virus has been robbed of its paralytogenic properties for man On the other hand, during the course of an epidemic caused by type 1 virus, Melnick & Ledinko [36] found an incidence of between six and 16 cases per 1,000 subclinical infections among children under 15 years of age, the lowest being in infants under one year of age and the highest in children aged between five and nine years.

Poliomyelitis viruses recovered from patients with paralytic poliomyelitis have generally been found to be more virulent in intracerebrally inoculated monkeys than those recovered from non-paralytic or minor illnesses [49] That is not to say that highly virulent strains have not been recovered from asymptomatic children, but it does suggest that high virulence by intracerebral inoculation in the monkey and paralytic disease *in man tend* to go together Accordingly, the paralytogenic activity of a virus in intracerebrally inoculated monkeys may be used as an orienting property in measuring the virulence of experimentally modified or naturally occurring strains of poliomyelitis virus. During the course of studies on different experimentally modified strains, I have come to recognize at least three distinct variations from the fully virulent parent virus in intracerebrally inoculated cynomolgus monkeys

(1) After inoculation of different dilutions of virus a varying proportion of monkeys over a wide range of dilutions either exhibit lesions without paralysis, or do not even show lesions Further intracerebral passage from one or more of the paralyzed monkeys uniformly produces the paralytic disease This phenomenon is interpreted as indicating that the original material consisted of a mixture of *fully virulent and modified virus.*

spectrum of this modified strain showed that while the largest doses of the human tissue-culture virus occasionally produced paralysis and almost regularly produced lesions in intracerebrally inoculated cynomolgus monkeys, this variant produced antibody with neither paralysis nor lesions in intracerebrally inoculated chimpanzees One of the four chimpanzees died of lobar pneumonia eight days after intracerebral inoculation of $10^{6.7}$ TCD_{50}, and, in addition to the absence of demonstrable CNS lesions, no virus was found in a suspension of medulla and of cervical and lumbar spinal cord. This is also the strain which readily infected (i e , produced antibody in) chimpanzees but not cynomolgus monkeys after oral and intramuscular administration of the virus The virus which was excreted in the stools by only one out of four orally infected chimpanzees (and by none out of seven in the intramuscular or intracerebral groups) also failed to produce paralysis in intracerebrally inoculated monkeys This is the strain which, in intracerebrally inoculated monkeys, yielded a "mutant" that regularly paralysed them, but no longer produced a cytopathogenic effect in epithelial cells or fibroblasts growing out of cynomolgus or human non-nervous tissue in vitro

Early in 1953 a study was undertaken in my laboratory to determine the conditions under which modifications in virulence can be produced by cultivation in non-nervous tissue To avoid the possibility that an induced change in virulence for the monkey might be due to the selective overgrowth of a variant more pathogenic for the host whose tissue was used in the culture rather than to the selecting influence of the non-nervous tissue, it was decided to keep the host constant Accordingly, the viruses were propagated in cynomolgus kidney tissue-culture, and all the quantitative tests for pathogenicity and immunogenicity were also performed in cynomolgus monkeys [51 53 57] The starting viruses were highly virulent strains of each of the three immunological types (Mahoney, Y-SK, and Leon) Mere cultivation in kidney tissue-cultures had no effect on virulence when the cultures were initiated with single or small numbers of virus particles, and when harvests were delayed for 24 hours or more after the appearance of cytopathogenic change Passage at 24-hour intervals with large inocula (10^5 to 10^7 TCD_{50}) produced culture fluids with diminished virulence and unusual patterns of response in cynomolgus monkeys, and purification of such culture fluids by the terminal dilution technique yielded what might be regarded as relatively avirulent variants of each of the three immunologic types Intracerebral titration of cultures of these variants in groups of four monkeys per dilution produced neither paralysis nor CNS lesions in any of the 84 monkeys used in the tests However, focal neuronal lesions, not associated with paralysis, were found in the spinal cord of three out of 48 monkeys inoculated intramuscularly with varying amounts of the Mahoney variant, in two of 20 receiving the Y-SK,

is now so limited to certain motor neurones, most of the virus particles or "seeds" introduced by intracerebral injection fall on the "rocks" of insusceptible tissue However, such a virus can still find, by accident of *inoculation in the muscle or the skin*, the projections of such neurones and thus invade the spinal cord; when it does so, in 1 of 20 or 40 monkeys it usually produces localized lesions without paralysis, but in an occasional animal it produces paralysis. The original character of the virus responsible for such an accident is proved by the fact that intracerebral passage yields negative results From the point of view of searching for the best "avirulent" virus to use for potential human immunization, preference would naturally be given to a variant that fails to produce paralysis even after direct spinal inoculation. It has been found, however, that modified viruses which behave like "spinal variants" in the cynomolgus monkey *are completely avirulent after direct spinal inoculation in chimpanzees.* A variant that is avirulent by the spinal route in monkeys as well as in chimpanzees would be preferred, but complete lack of virulence for chimpanzees might constitute an adequate final test for a strain that is being considered for use in human beings

The first experimental modification of the virulence of a poliomyelitis virus was obtained by Theiler[64] when he found that after 50 *rapid* intracerebral passages in mice, the Lansing strain no longer produced signs of poliomyelitis in eight intracerebrally inoculated monkeys Whether the "rapidity" of passage, or accidental overgrowth of a mutant, or both, were responsible for this is not known, but no such loss of virulence occurred in other laboratories where the same strain had undergone 200 or more passages in mice More recently Gear[20] confirmed Theiler's observation by submitting the Lansing virus to a number of rapid passages through *Mystromys irrorattus*, a rodent of the South African veld In the hundredth passage Gear observed that it still produced paralysis in one out of ten intracerebrally inoculated monkeys, and one wonders whether the mouse-passed virus was still a mixture of the original virulent virus and the modified virus, or whether a "spinal variant" or other type of mutant was involved. The same questions must be asked about the limited pathogenicity of the type 2 TN strain used in the human feeding experiments by Koprowski, Jervis & Norton,[29] of the mouse-pathogenic type 1 Mahoney mutant picked up by Li & Schaeffer,[31] and of the type 2 MEF_1 variant adapted to chicken-embryos by Cabasso et al.[11]

Enders, Weller & Robbins[17, 18] first reported that the type 1 Brunhilde strain had been modified in its virulence for monkeys after a number of passages in human non-nervous tissue. After two terminal dilution passages, intracerebral inoculation of $10^{5.8}$ 50% tissue-culture cytopathogenic doses (TCD_{50}) produced paralysis in two out of nine monkeys. More extensive studies in my laboratory[51] on the pathogenic and immunogenic

spectrum of this modified strain showed that while the largest doses of the human tissue-culture virus occasionally produced paralysis and almost regularly produced lesions in intracerebrally inoculated cynomolgus monkeys, this variant produced antibody with neither paralysis nor lesions in intracerebrally inoculated chimpanzees One of the four chimpanzees died of lobar pneumonia eight days after intracerebral inoculation of 10' TCD_{50}, and, in addition to the absence of demonstrable CNS lesions, no virus was found in a suspension of medulla and of cervical and lumbar spinal cord. This is also the strain which readily infected (i e , produced antibody in) chimpanzees but not cynomolgus monkeys after oral and intramuscular administration of the virus The virus which was excreted in the stools by only one out of four orally infected chimpanzees (and by none out of seven in the intramuscular or intracerebral groups) also failed to produce paralysis in intracerebrally inoculated monkeys This is the strain which, in intracerebrally inoculated monkeys, yielded a "mutant" that regularly paralysed them, but no longer produced a cytopathogenic effect in epithelial cells or fibroblasts growing out of cynomolgus or human non-nervous tissue in vitro

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and in none of 40 inoculated with varying amounts of the Leon virus Virus recovered from the spinal cord of one of these monkeys produced no paralysis on intracerebral passage in monkeys. It was assumed that these variants possessed a limited capacity to affect the motor neurones when they were directly invaded, and actual test by intraspinal injection in monkeys revealed that these modified viruses were "spinal variants". The extent of viral multiplication after direct spinal injection in monkeys varied with the different strains, but in most instances it was not sufficient to permit a second passage to other monkeys

The modified viruses propagated in kidney culture yielded titres of approximately 10^7 TCD_{50} per ml, as measured by cytopathogenic activity on epithelial cells growing out of kidney tissue in vitro, but no pathological changes were found in the muscles, kidneys, testes, ovaries, adrenals, heart, pancreas, spleen, or liver of intramuscularly inoculated cynomolgus monkeys. Antibody appeared in the intramuscularly inoculated monkeys, but the failure of a varying proportion of animals to develop antibody after inoculation with the smaller doses indicated that the capacity for extraneural multiplication in the monkey was less than that of the virulent parent strains The original type 1 (Mahoney) virus produced paralysis in approximately 60% of the monkeys after ingestion of $10^{6.7}$ TCD_{50} once a day for three days Feeding ten times as much of the modified virus produced neither paralysis nor lesions, but did give rise to both antibody and resistance to oral challenge with the virulent virus The type 1 (Mahoney) and type 2 (Y-SK) variants produce paralysis in mice after spinal inoculation, while the type 3 (Leon) variant does not Spinal inoculation of these variants into 11 chimpanzees produced neither paralysis nor lesions

A single feeding of 0 5-1 ml of culture fluid of each of the three types of the experimentally segregated chimpanzee-avirulent viruses produced a rapid immunogenic infection in seven of nine chimpanzees When a mixture of all three viruses was fed to two chimpanzees, the type 1 and type 2 antibodies developed rapidly, while the response to the type 3 was suppressed However, when the same mixture was injected intramuscularly, in one-tenth of the dose, both chimpanzees developed antibodies to all three types Tests on human adult volunteers indicated that the type 2 and type 3 chimpanzee-avirulent strains can multiply in the human alimentary tract even in individuals who possess low titres of naturally acquired homotypic antibody, and that such infection is followed by a rise in antibody titres

No viraemia was detected in the 21 chimpanzees which received the various modified viruses by mouth or intramuscularly. Poliomyelitis virus was found in the stools at seven to 28 days in nine of the 15 orally infected chimpanzees, but in none of the six which received the viruses intramuscularly. If further work should substantiate the current indications

that by the intramuscular route immunity can be produced (*a*) more regularly, (*b*) with smaller doses, and (*c*) without excretion of virus, one would have to weigh these advantages against the simplicity of immunization by the oral route. The characteristics of the virus excreted by the nine chimpanzees and the two human volunteers were tested by intracerebral inoculation in monkeys. In nine of these tests the indications are that no intracerebrally virulent mutants arose in the chimpanzee or human alimentary tracts, but further tests need to be performed with the virus progeny derived from the stools of at least two chimpanzees to establish whether or not such mutants may appear.

The currently available strains of each of the three immunologic types which produce neither paralysis nor lesions after injection into the spinal cord of chimpanzees should receive further investigation as potential candidates for human immunization Among these strains, however, there are some which in spinally inoculated monkeys produce only very mild and localized paralysis and even this quite irregularly, while others produce paralysis more regularly and more extensively. The five naturally occurring type 2 and type 3 strains which were recovered from healthy children produced paralysis more regularly and extensively in spinally inoculated monkeys than the Y-SK and Leon strains which we segregated experimentally. From now on, therefore, the latter are the strains of choice for the type 2 and type 3 viruses to be used in further studies on human beings. Among the type 1 modified viruses we made a quantitative comparison of the Brunhilde strain propagated in human tissue by Enders and his associates[18] and then in our own laboratory in monkey kidney tissue,[51] of the Mahoney strain segregated in tissue culture, and of the Mahoney strain segregated in mice by Li & Schaeffer.[31] Since we found that the Li & Schaeffer strain produced the least paralysis in spinally inoculated monkeys, further studies were carried out with the progeny of individual terminal dilution tubes, and we recovered a strain which only rarely produces paralysis, and that of a very mild and transitory nature This special variant of the Li & Schaeffer strain would therefore be the best currently available type 1 candidate, if studies on chimpanzees should show that it has not lost its immunogenic capacity While the search is continuing for strains which are completely avirulent by the spinal route in monkeys as well as in chimpanzees, further progress can be made by using the currently available strains for the orienting, quantitative studies which will indicate the best procedure for active immunization of human beings Using fixed seed lots of these strains, it has been possible to demonstrate sufficient genetic stability in tissue culture to permit their use for practical purposes

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No viraemia was detected in the 21 chimpanzees which received the various modified viruses by mouth or intramuscularly. Poliomyelitis virus was found in the stools at seven to 28 days in nine of the 15 orally infected chimpanzees, but in none of the six which received the viruses intramuscularly. If further work should substantiate the current indications

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IMMUNIZATION OF MAN WITH LIVING POLIOMYELITIS VIRUS

HILARY KOPROWSKI, M D.

Assistant Director, Viral and Rickettsial Research, Lederle Laboratories Division, American Cyanamid Company, Pearl River, N Y , USA

> "And when our signs are recited to them they say 'This is only a man who wishes to turn you from what your fathers served ; and they say 'This is only a lie forged', and those who misbelieve will say of the truth when it comes to them 'It is only obvious sorcery'"
>
> *The Koran, the Chapter of Seba*

The initial studies on the immunization of human subjects with an orally administered attenuated strain of poliomyelitis virus were undertaken to demonstrate the safety of the procedure, and to determine the degree of the elicited antibody response.

Material and Methods

Virus

The TN strain of poliomyelitis is a type 2 virus isolated during attempts to adapt the Brockman strain (type 1) to mice After passages through mice, cross-neutralization tests in mice and cotton-rats showed the TN strain to be identical with type 2 virus Data summarized in table I show that at the eighth mouse-brain-passage level the TN strain had a remarkably low degree of virulence for intracerebrally inoculated monkeys This characteristic was retained after the virus was adapted to cotton-rats provided it was kept at low passage levels, but prolonged cultivation of the TN strain in cotton-rats resulted in enhancement of its pathogenic properties However, for rhesus monkeys it remained less pathogenic than [illegible]

[illegible] of the pathogenic properties of a virus maintained in cotton-rat central nervous system (CNS) merits further attention, but is not pertinent to the present study.

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Human subjects

The prime criterion for the selection of individuals who were to receive the TN virus was that they be susceptible to type 2 infection, as indicated by the absence in their blood of neutralizing antibodies against type 2.

TABLE II. RESULTS OF IMMUNIZATION OF MAN AGAINST POLIOMYELITIS VIRUS WITH LIVE VIRUS ADMINISTERED ORALLY

Clinical trial group	Number of subjects	Pre-immunization studies				Post-immunization studies	
		number of sera showing presence of antibodies against virus types			number of subjects with no antibodies against any type of virus	number of subjects excreting virus in faeces *	number of subjects developing antibodies against type-2 virus
		1	2	3			
A **	20	{ 5 { 2	0 4	2 } 0 }	10	12 2	16 —
B	61	43	0	37	6	31	53 (+8) ††
C	5 †	3	0	0	2	0	4
D	3 †	0	0	3	0	2	3
Total	89	53	4	42	18	47	76 (+8) ††

* For definition of an intestinal carrier, see footnote c, page 333

** Bracketed figures are broken down to indicate the four individuals who had type 2 antibodies before feeding

† Included in this group are subjects who received simultaneously immune-serum globulin and virus (see text)

†† Subsequent development of antibodies in these 8 individuals has been described in the text

In addition, an attempt was made to secure as many individuals as possible whose blood contained no antibodies against any of the three types of virus [b] It was relatively easy to find subjects who had no antibodies against type 2. This was true for 85 individuals out of 89 (table II) It was more difficult to secure a large number of persons who had no antibodies against the other two types of virus, and only 18 such individuals were found among the 85, as shown in table II The 89 were divided into four trial groups two major groups, A and B, and two small groups, C and D

[b] Although the serological studies were based in most cases on mouse neutralization tests negative results were reappraised in several instances by tissue-culture neutralization tests The results of the latter in which a small (10-30 cytopathogenic units) dose of virus was employed fully confirmed the data obtained in the mouse neutralization tests

TABLE I. INTRACEREBRAL INOCULATION OF RHESUS MONKEYS WITH TN STRAIN AT DIFFERENT PASSAGE LEVELS

Passage	PD_{50} titre range in mice *	Cumulative results of inoculation of monkeys					Feeding of man	
		degree of paralysis			attack-rate **	mortality-rate	clinical trial group	number of subjects fed
		none **	moderate	severe				
8 MB	3 10	18	0	0	0/18	0/18	—	0
1–4 CR	1 10–4 00	169	14	0	25/183	0/183	A †	9 } 70
							B	53
							C	5
							D	3
12–17 CR	1 10–3 40	26	3	1	4/30	0/30	—	0
32–35 CR	3 50–4 50	61	46	23	76/130	22/130	A	11 } 19
							B	8
30 CR + 30 BH	6 20	9	1	0	1/10	0/10	—	0

* Negative log to the base 10

** Monkeys showing signs of mild form of disease, e g , tremor and/or fever, are included in these columns

† See table II

MB = Mouse brain passage

CR = Cotton-rat brain passage

BH = Baby hamster brain passage

Neither the mouse- nor the cotton-rat-adapted TN strain showed any cytopathogenic effect on monkey (cynomolgus) kidney epithelium or testicular fibroblasts, but after one or two passages of the virus in tissue culture this property changed In some instances monkeys which had shown signs of paralysis were sacrificed and their spinal-cord tissues were subinoculated into tissue cultures and into monkeys Invariably, presence of virus was detected either by direct cytopathogenic effect or, more frequently, by blind passages in tissue culture, but serial dilutions of cord tissue failed to elicit signs of sickness in intracerebrally inoculated monkeys

Before proceeding to a trial in human subjects, we further appraised the antigenic properties of the virus First, monkeys which had remained symptom-free after intracerebral inoculation with the TN strain were challenged with virulent homologous virus and were found to be immune.[a 20] Second, chimpanzees to which the TN strain had been orally administered proved to have developed neutralizing antibodies[16] It thus became evident that the TN strain, after passage through mice and/or cotton-rats, had only a slight residual virulence for the nervous system of the monkey but had retained its antigenic quality

were all stools assayed for the presence of the virus; in most cases stools were collected every three or four days Thus, if any virus was excreted during the intercollection period, it could have been missed. The use of the mouse as a test animal may also have contributed to the determination of a rather low carrier-rate. Therefore, the figure should be considered as a *minimum* number of individuals who became intestinal carriers of the virus.

Viraemia

If one accepts the currently expounded concept of the pathogenesis of poliomyelitis,[1] the presence of virus in the blood should be considered a factor of paramount importance in the evaluation of the safety[d] of any given immunization procedure. In view of this fact, individuals in trial groups B and C (see table II) were bled at intervals, as shown in table III.

TABLE III. ASSAY FOR PRESENCE OF VIRUS IN BLOOD

Trial group	Number of subjects	Schedule of blood collections *	Number of positive isolations	*Intestinal* carriage-rate
B	30 31	1, 3, 5, 7, 9, 11 2, 4, 6, 8, 10, 12	0 0	15/30 15/31
C	2 3	1, 2, 3, 4, 5, 6, 7, 8 5, 6, 7, 8	0 0	0/2 0/3

* Considering day of administration of virus as 0 day

Assay of the blood specimens revealed no evidence that virus was present, regardless of the carrier state of the donors. The query may then be raised as to whether the mouse, as test animal, represents a sufficiently sensitive subject for virus assay. All blood samples obtained from several individuals who became intestinal carriers of the virus were reappraised for the presence of virus by subinoculation in large volume into *tissue-culture* preparations, following techniques recently described.[12] Included in this reassay were samples of blood from six individuals who had had no demonstrable neutralizing antibodies against any of the three types of poliomyelitis virus before the administration of the TN strain (see group B, table II) Despite numerous attempts to isolate the virus from these samples of blood by means of blind passages, no cytopathogenic effects were observed in tissue culture

[d] This means the absence of clinical symptoms of illness following the administration of an active virus

Method of administration

Although differences in opinion on the pathogenesis of poliomyelitis in man still persist, nonetheless the theory that the mouth is the portal of entry and that the mucosa of the intestinal tract aid in the multiplication of the virus has gained considerable support in recent times[3] The TN virus was therefore administered by the oral route, either by stomach-tube or by direct feeding Another reason for giving preference to the oral route over the parenteral was the possibility that a subcutaneous or intramuscular inoculation, regardless of the virus content of the inoculum, might of itself induce paralysis in a person already undergoing an incubation period of poliomyelitis Accidents of this nature have been reported in immunization against diphtheria and whooping cough[22, 25]

The material for oral administration consisted of infected cotton-rat brain and spinal-cord tissue made into a 20% suspension in distilled water. Table I indicates the number of subjects receiving virus stemming from various passage levels Amounts of 10, 5, or 1 ml were given, the majority of the individuals receiving 5 ml The suspension was either fed by stomach-tube or diluted in one or two ounces of milk, or chocolate milk, and fed in one session The first human subject was fed the virus by stomach-tube on 27 February 1950,[14] and in the complete absence of any signs of illness associated with the establishment of intestinal carriage,[c] a decision was reached to feed the virus to additional subjects. In the course of the three years following, 88 more persons received the virus orally[15, 19]

Results

It should be categorically stated that in none of the human subjects were any signs or symptoms of illness noted which could have been attributed to the ingestion of the virus Clinical observations were conducted under very strict surveillance on a 24-hour basis for three weeks after administration of the virus, and most of the individuals remained under clinical observation for one year or longer Temperatures were determined frequently, but no significant rises in body temperature in any of the 89 subjects were recorded. In addition, experienced observers examined the patients for possible manifestations of disturbances of either the central or peripheral nervous system, of the muscular apparatus, or of the gastro-intestinal tract. None were noted

As is apparent from the data in table II, not all the recipients of the virus became intestinal carriers *However, only in a relatively few cases*

[c] In this and subsequent cases, an individual was defined as a "carrier" if virus was isolated from the stool specimens collected either on the fifth day after oral administration or at any time thereafter

[illegible] n period,
[illegible] the sera
[illegible] 1 and 3
when the immunization programme began (table IV) developed no such antibodies. A further refutation of the "multiple exposures" argument lies in the immunological response of subjects No 10, 13, and 14 (see table IV), who had received the virus only once[15] but whose response was similar in magnitude and duration to that of the other subjects who had received multiple feedings of the TN strain

It is reasonable to assume that the period of immunity may extend beyond the three years covered in this trial, and a long-term study of the serological status of the individuals is contemplated

Antibody level and protection

The decisive test of the protective value of this immunization procedure would obviously be an exposure to a severe epidemic of poliomyelitis. In view of the small number of subjects who were fed the virus, it seems most unlikely that such an opportunity for a natural challenge will ever present itself On the other hand, some information may be gained by comparing the antibody levels shown in table IV with those engendered passively through the administration of immune-serum globulin and found necessary to protect either chimpanzees or cynomolgus monkeys[2, 4] against paralysis induced by the oral administration of a virulent virus. These data indicate that a 1/2 - 1/10 titre of circulating passive antibody was found to be adequate to protect the animals against the viraemia and subsequent paralysis observed in the controls. Because of the greater susceptibility of the human species to poliomyelitis infection (see below), application of results obtained in cynomolgus monkeys to human prophylaxis is questionable, but the antibody level elicted in man by the oral administration of TN virus would probably be adequate for protective purposes This antibody level, however, did not completely prevent intestinal carriage of the virus. The TN strain was re-administered to 12 subjects in trial group A[15] (see table II), of whom ten had been found to excrete virus after the first feeding Ten of the 12 individuals failed to become carriers after the second feeding Of the other two, one became a carrier twice, and one three times, after successive feedings of the virus and in the presence of high antibody titre On the other hand, one of the subjects who had had homotypic antibodies originally received four large feedings of the virus at daily intervals with no demonstrable evidence of intestinal carriage[15]

From the foregoing it is apparent that serological immunity induced by oral administration of virus is not always paralleled by protection of the intestinal tract against infection with homotypic virus

Immunity and persistence of antibodies

Data presented in the last column of table II indicate that an overwhelming number of the subjects responded to the antigenic stimulus of the active virus. Positive evidence that homologous antibodies had developed was obtained as early as seven days after oral administration of the virus, and most of the serum specimens obtained one month after administration contained antibodies.[f]

Eight individuals in trial group B seemed to remain immunologically unresponsive [19] Close re-check of the clinical condition of these eight patients revealed an extremely low-grade mental development, particularly evidenced by peculiar eating habits Doubt arose as to whether the virus had been ingested To make certain of exposure, these individuals were re-fed the virus under proper supervision ten months after the first feeding, with most gratifying results. All eight became carriers, and all developed antibodies within one month after the re-administration of the virus. A ninth member of group B, who had become a carrier and had developed antibodies after the first feeding of the virus, was also re-fed No virus was isolated after the second feeding from the stools of this individual, nor was any change observed in the level of homologous antibodies present in his blood

As might have been expected, the antibody levels varied considerably among the individuals Results of serological tests did not reveal any significant differences in antibody response following one or multiple feedings of the virus. The appearance of homologous antibody against type 2 in no way influenced the serological status in relation to the other two types of virus, and those subjects who had previously had no antibodies against any type of virus developed them only against type 2.

The uniform response of individuals in trial group A to the administration of the TN virus [15] made it possible, through long-term observation of 14 out of the original 20, to gain information about the persistence of antibodies.[17] As the data summarized in table IV show, the homotypic antibody level [f] remained essentially unchanged in the blood of all subjects, with the possible exception of No 8, for periods extending from 26 to 41 months after oral administration of the virus. It may be argued that this persistent immune response, rather than being the result of the original antigenic stimulus, could have been maintained by inapparent re-exposures to type 2 virus. However, it seems most unlikely that exceptive

contacts could have taken place during the three-year observation period, with exposures limited to type 2 and none to types 1 and 3; yet the sera of 9 out of 14 subjects who had had no antibodies against types 1 and 3 when the immunization programme began (table IV) developed no such antibodies. A further refutation of the "multiple exposures" argument lies in the immunological response of subjects No 10, 13, and 14 (see table IV), who had received the virus only once [15] but whose response was similar in magnitude and duration to that of the other subjects who had received multiple feedings of the TN strain

It is reasonable to assume that the period of immunity may extend beyond the three years covered in this trial, and a long-term study of the serological status of the individuals is contemplated.

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The decisive test of the protective value of this immunization procedure would obviously be an exposure to a severe epidemic of poliomyelitis In view of the small number of subjects who were fed the virus, it seems most unlikely that such an opportunity for a natural challenge will ever present itself On the other hand, some information may be gained by comparing the antibody levels shown in table IV with those engendered passively through the administration of immune-serum globulin and found necessary to protect either chimpanzees or cynomolgus monkeys [2, 4] against paralysis induced by the oral administration of a virulent virus These data indicate that a 1/2 - 1/10 titre of circulating passive antibody was found to be adequate to protect the animals against the viraemia and subsequent paralysis observed in the controls Because of the greater susceptibility of the human species to poliomyelitis infection (see below), application of results obtained in cynomolgus monkeys to human prophylaxis is questionable, but the antibody level elicted in man by the oral administration of TN virus would probably be adequate for protective purposes This antibody level, however, did not completely prevent intestinal carriage of the virus The TN strain was re-administered to 12 subjects in trial group A [15] (see table II), of whom ten had been found to excrete virus after the first feeding Ten of the 12 individuals failed to become carriers after the second feeding. Of the other two, one became a carrier twice, and one three times, after successive feedings of the virus and in the presence of high antibody titre On the other hand, one of the subjects who had had homotypic antibodies originally received four large feedings of the virus at daily intervals with no demonstrable evidence of intestinal carriage.[15]

From the foregoing it is apparent that serological immunity induced by oral administration of virus is not always paralleled by protection of the intestinal tract against infection with homotypic virus

TABLE IV. PERSISTENCE OF ANTIBODIES AGAINST TYPE 2 POLIOMYELITIS VIRUS IN SERA

Subject No	Oral administration of virus		Neutralization test	Minimum protective titre of sera (months after oral adminis							
	number of feedings	months between first and last feeding		0	1	2	3	4	11	12	14
2	2	1	a b c	1/6	1/22	1/90 1/74 1/220					
3	3	3	a b c	< 1/2 < 1/2	1/15		1/75				
4	3	3	a b c	< 1/2	1/38		1/141 1/43				
5	3	3	a b c	1/4 1/4	1/514		1/250 1/526				
6	2	2	a b	< 1/2 < 1/2	1/200			1/200 1/600			
7	2	2	a b c	1/3	1/302		1/426 1/100				
8	2	2	a b	1/3 1/3	1/200	1/266	1/200 **		1/15 **		
9	2	2	a b c	< 1/2 †	1/422		1/390 1/290				[illegible]
10	1	—	a b c	< 1/2 ** < 1/2 1/2	1/111 1/1186					1/692 1/200	
12	2	3	a b c	< 1/2 ** < 1/2 < 1/2	1/386 1/332						
13	1	—	a b c	< 1/2 < 1/2 < 1/2	1/32 1/14					1/20 1/28	
14	1	—	a b c	1/15 ** 1/12 1/7	1/378 1/72 1/200						
16	4	10	a b	< 1/2 < 1/2		1/218				1/91	
17	3	8	a b c	< 1/2 < 1/2	1/200	1/242					

Results

SERA OF 14 SUBJECTS FED TN STRAIN IN TRIAL A (SEE TABLE II)

of serum obtained
administration of virus)

14	15	18	20	26	27	28	29	33	34	36	41
			1/656							1/640 *	
		1/39 1/118							1/100 *		
		1/31 1/34							1/28 *		
		1/148 1 93							1/60 *		
				1/121 *							
	1/39 1/98						1/90 *				
1/75 1/380						1/320 †					
				1/280 **							
					1/100 1/520						1/96 **
						1/60 *					
					1/74 **						
								1/60 *			
			1/200 1/280						1/94 *		

* absence antibodies
** p tibodies against type 1 virus
odies against types 1 and 3

TABLE IV. PERSISTENCE OF ANTIBODIES AGAINST TYPE 2 POLIOMYELITIS VIRUS IN

Subject No	Oral administration of virus		Neutralization test	Minimum protective titre (months after oral						
	number of feedings	months between first and last feeding		0	1	2	3	4	11	12
2	2	1	a b c	1/6	1/22	1/90 1/74 1/220				
3	3	3	a b c	< 1/2 < 1/2	1/15		1/75			
4	3	3	a b c	< 1/2	1/38		1/141 1/43			
5	3	3	a b c	1/4 1/4	1/514		1/250 1/526			
6	2	2	a b	< 1/2 < 1/2	1/200			1/200 1/600		
7	2	2	a b c	1/3	1/302		1/426 1/100			
8	2	2	a b	1/3 1/3	1/200	1/266	1/200 **		1/15 **	
9	2	2	a b c	< 1/2 †	1/422		1/390 1/290			
10	1	—	a b c	< 1/2 ** < 1/2 1/2	1/111 1/1186					1/692 1/200
12	2	3	a b c	< 1/2 ** < 1/2 < 1/2	1/386 1/332					
13	1	—	a b c	< 1/2 < 1/2 < 1/2	1/32 1/14					1/20 1/28
14	1	—	a b c	1/15 ** 1/12 1/7	1/378 1/72 1/200					
16	4	10	a b	< 1/2 < 1/2		1/218				1/91
17	3	8	a b c	< 1/2 < 1/2	1/200	1/242				

Results of neutralization tests against types 1 and 3 ind

evident, however, that intestinal infection can be induced with very small amounts of virus, and that very small amounts will also elicit the formation of homologous antibodies in the blood

Effect of passive immunity

Two of the five members of group C (see table II) were fed a mixture of virus and immune-serum globulin of human origin. This mixture had been found to be avirulent for mice infected intracerebrally. Neither person developed a carrier state, and only one of them developed homologous antibodies Three other subjects, who had been fed at the same time with the same amount of virus but without the immune-serum globulin, showed no evidence of intestinal carriage, but did develop antibodies.

TABLE VI EFFECT OF PASSIVE IMMUNITY UPON RESPONSE TO ACTIVE VIRUS

Subject	Dose of virus (ml)	Source of passive antibodies	Intestinal carriage of virus	Serum antibody titre (days after administration of virus)						
				0	1	3	6	7	21	28
C	5	Injection of immune globulin *	0	< 1/2	< 1/2	Trace **		1/90	1/512	1/512
St	None	Injection of immune globulin *	—	< 1/2	< 1/2	Trace **	< 1/2	< 1/2		
S	1	None	+	< 1/2						1/22
M	1	Maternal	+	1/6						1/2,048

* 0 1 ml per kg of body-weight, injected intramuscularly at the time of oral administration of virus

** Partial prevention of cytopathogenic effect of the virus was noted in tissue-culture tubes inoculated with undiluted serum

0 = negative — = no result + = positive

The results of another trial, summarized in table VI, are perhaps of some interest, although they have a rather meagre statistical value Subject C received immune-serum globulin parenterally, as did St , and the former was fed virus simultaneously It is interesting to note that traces of neutralizing antibodies on the third day after administration of human globulin were the only indication of passive immunity in these subjects.

It is also quite clear that this did not prevent the development of active immunity, noticeable in individual C as early as seven days after administration of the virus and globulin

The probable presence of maternal passive immunity in the blood of one subject, M , three months old at the time of virus feeding, failed to

Concentration of virus in inoculum

Although most individuals in trial groups A and B were given a single 5-ml dose of a 20% suspension of infected cotton-rat brain and cord tissue, in some cases the amount of virus-inoculum was decreased to one ml. Three subjects in group A (see table V) were fed different amounts from the same virus pool [15] Intestinal carriage was established in the two individuals who received 5 ml and 10 ml of the virus suspension, respectively. No virus was recovered from the stool specimens of the subject fed 1 ml of the virus. However, homologous antibodies were found at approximately the same level in the blood samples of all three individuals

TABLE V. RELATION BETWEEN THE AMOUNT OF INGESTED VIRUS, CARRIER STATE, AND ANTIBODY RESPONSE

Trial group	Subject no	Amount of virus administered orally * (ml)	Collection of stools (days after feeding)	Isolation of virus from stools (days after feeding)	Antibody level	
					before administration of virus	after administration of virus **
A	4	10	4, 7, 10, 14, 17, 24	4, 7, 10	< 1/2	1/260
	3	5	4, 7, 10, 14, 17, 24	4, 7, 10, 14	< 1/2	1/120
	5	1	4, 7, 10, 14, 17, 24	none	1/4	1/514
D	67	1	2, 3, 4, 6, 9, 11, 14, 16, 20, 23, 25, 29	2, 3, 4, 6, 9, 11, 16, 20, 25	1/6	1/2,048
	68	1	4, 7, 11, 18, 21, 22	11, 18, 21, 22	< 1/2	1/22
B	40	5	6, 9, 12, 15, 18, 20, 23	12, 15, 18, 20	1/3	1/105

* In the form of a 20% suspension of cotton-rat spinal-cord and brain tissue
** 30 days

Even better evidence of the infective potency of 1 ml of virus was obtained in two subjects of group D (67 and 68) who developed evidence of intestinal carriage after oral administration of this amount of the TN strain (see table V). The carrier-rate of subject 68 equalled, and that of 67 surpassed, that of one member of group B who had received 5 ml of virus suspension from the same pool. Again, no marked differences in serological response were noted in relation to doses of different amounts of virus

Administration of the virus resuspended in milk gave as good results as feeding through a stomach-tube. It is beyond the scope of the present paper to discuss various dosage schedules of the virus for man It is quite

As far as the virulence of a strain of poliomyelitis virus is concerned, it is customarily determined in terms of the capacity of the virus to produce clinically discernible signs of CNS involvement in the monkey More recently, it has become the practice to term a strain "avirulent" or "attenuated" if it causes a high incidence of infection in rodents and/or tissue culture but is accompanied by little or no incidence of paralysis in intracerebrally injected monkeys

Two questions are pertinent at this point. Is the absence of intracerebral pathogenicity for monkeys an indication of avirulence for human beings? Conversely, will a virus remain a menace to man if it is still pathogenic for monkeys injected intracerebrally? Before attempting to answer, or—what is perhaps the better part of valour—to evade, both questions, it might be well to discuss briefly the comparative susceptibility of man and monkey to poliomyelitis virus

TABLE VII RESULTS OF ORAL ADMINISTRATION OF TN STRAIN TO THREE SPECIES OF PRIMATE*

Pool No	Species	Dose of virus (ml)	Total number fed	Number excreting virus	Number showing anti-bodies	Range of antibody titre
16	Man Chimpanzee	1, 5, or 10 10	9 2	7 1	9 2	1/20–1/500 1/85–1/95
21 23 24	Man	10 10 5 or 10	2 5 8	1 3 5	2 5 8	1/60–1/700 1/32–1/2,500 1/10–1/600
F_1	Chimpanzee	2×10	3	1	3	1/7 –1/300
31	Man Chimpanzee Cynomolgus Cynomolgus	5 10 3×2 2×6	54 4 11 5	31 0 0 0	54 4 0 0	1/15–1/500 1/2 –1/35
YHP N-63	Cynomolgus	3×2	5	1	2	1/2
Grand total	Man Chimpanzee Cynomolgus		78 9 21	47 2 1	78 9 2	

* In no instance included in this table were signs of illness noted

interfere with the establishment of intestinal carriage, and may even have enhanced the active response to the virus, as indicated by the unusually high titre of neutralizing antibodies.

Reflections

"the craft so long to lerne.."
Chaucer

Passing from the experimental to the speculative point of view, we are faced with this question: What are the fundamental characteristics of a living agent which determine its acceptance as a vaccine? Recently, against a background of experimental observations obtained in poliomyelitis and other viral diseases, such characteristics for an attenuated strain of virus were defined and divided into four categories.[13]

(1) inability of the virus to produce serious illness in the vaccinated host,

(2) non-transmissibility of the virus from an "infected" to a non-infected host; or, if transmission occurs, fixation of the modified properties;

(3) presence of sufficient amount of living virus in a final product to meet minimum titre requirements,

(4) evidence of adequate antigenicity following a single administration of the virus

All the foregoing characteristics are of fundamental importance, but (1) and (2) embody the main criteria for adjudging an attenuated virus as suitable for use as an immunizing agent.

In veterinary medicine it is relatively easy to prove the "safety" of an attenuated virus preparation. Inoculation of the natural host without mishap presents convincing proof In human prophylaxis it is a different matter. Although one would not hesitate to expose man directly to infection with unattenuated forms of such naturally-occurring mild viruses as those of German measles, mumps, or chicken-pox, it would be clearly undesirable to do so with poliomyelitis virus The criteria of safety for the latter present a formidable problem, since the degree of attenuation must be evaluated by laboratory observations, i e, the results of inoculation of experimental animals. One should recall that a universal criterion of safety, applicable equally to all attenuated viruses, is a myth readily dispelled by consideration of the wide variation existing among attenuated viruses For instance, just as the epidemiology, clinical [illegible]
d
n

of poliomyelitis virus.

TABLE VIII. VIRULENCE OF SM RODENT-ADAPTED STRAIN OF POLIOMYELITIS (TYPE I) FOR MONKEYS

Inoculum					Paralytic ratio of monkeys injected intracerebrally with dilutions of virus							
host *	passage no	PD_{50} titre ** in		TD_{50} † titre	10^{-0}	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	monkey species
		mice	cotton-rats									
Cotton-rat	12 + 11 TC	2 75	N T	6 70	2/4	4/4	4/4	3/4	1/4	0/4	0/4	Java
	16	2 80	N T	5 50	—	8/10	1/2	2/2	1/2	2/2	—	rhesus
Mouse (Swiss strain)	12	2 75	N T	5 50	—	0/5	—	—	—	—	—	rhesus
	22	< 1 00 ††	2 15	4 50	—	2/4	0/3	0/2	0/2	0/2	0/2	rhesus
	35 + 1 TC	N T	N T	6 00	1/3	1/3	0/3	0/3	—	—	—	rhesus
Mouse (PRI strain)	22 + 1 TC + 1 mouse	2 00	< 1 00	5.20	—	0 4	0/4	0/4	0/4	0/2	—	Java

* *Virus previously passaged through 3 Swiss albino and 4 PRI mice*
** Expressed as negative log to the base 10
† *Cytopathogenic effect in tissue culture*
†† Mice found paralysed at 10^{-1} dilution
TC = Tissue culture passage
N T = Not tested

These results cannot be generalized, because of the nature of the TN strain, but it is possible to postulate that there are strains of poliomyelitis virus (entirely devoid of virulence for monkeys even when injected intracerebrally) which are yet capable of infecting the human intestinal tract Such strains, perhaps, should have preference for use in human immunization over those which have paralysis-producing properties for monkeys. However, if for some reason or other a strain still pathogenic for monkeys should be indicated as an immunizing agent for man, it should not necessarily be regarded as "unsafe". The 17D yellow-fever strain and living *rabies virus are still pathogenic for intracerebrally injected monkeys, yet* both viruses seem to be devoid of pathogenicity when injected parenterally into man [13]

Where Do We Go from Here?

"Come down, O Maid, from yonder mountain height"

Tennyson

We stand in need of two things one is a stockpile of "attenuated" poliomyelitis viruses, strains representing all three types, preferably devoid of excessive neurotropism (see below), the other is more adequate criteria of safety, applicable to man himself, which will eliminate the hazards of an immunization procedure Reliance solely on data obtained *after* the vaccination of a great number of subjects is inadequate

Increased activity in recent years in poliomyelitis research has resulted in the availability of more and more strains which qualify as "attenuated" *variants. In addition to the TN strain, type 2 is represented by the egg-*adapted variant of the MEF1 strain [8, 9, 27] of markedly diminished virulence for the nervous system of either cynomolgus or rhesus monkeys [9] The pathogenic range of another type 2 strain (Y-SK) has been changed through rapid serial passages in tissue culture,[28] and the resulting variant seems also to be "attenuated" The Mahoney strain of type 1 poliomyelitis appears to have lost most of its pathogenic properties for monkeys after its adaptation to mice,[23] as did the same strain after rapid passages in tissue culture [28]

The mechanism of attenuation will remain an enigma as long as the complex process of virus-cell interaction defies comprehension Current work with influenza virus [7] *suggests that virulence is determined by the* distribution of certain genetic units in a viral population Thus one may speculate that attenuation of poliomyelitis virus may occur when virus particles become endowed with *genetic unit distribution differing from that* which obtained in the original "virulent" strain It is also conceivable that, without "redistribution" of the genetic units, the surface properties of the virus particles become imbued in the process of attenuation with

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		mice	cotton-rats									
Cotton-rat	12 + 11 TC	2 75	N T	8 70	2/4	4/4	4/4	3/4	1/4	0/4	0/4	Java
	16	2 80	N T	5 50	—	8/10	1/2	2/2	1/2	2/2	—	rhesus
Mouse (Swiss strain)	12	2 75	N T	5 50	—	0/5	—	—	—	—	—	rhesus
	22	< 1 00 ††	2 15	4 50	—	2/4	0/3	0/2	0/2	0,2	0/2	rhesus
	35 + 1 TC	N T	N T.	6 00	1/3	1/3	0 3	0/3	—	—	—	rhesus
Mouse (PRI strain)	22 + 1 TC + 1 mouse	2 00	< 1 00	5 20	—	0/4	0/4	0/4	0/4	0/2	—	Java

* Virus previously passaged through 3 Swiss albino and 4 PRI mice
** Expressed as negative log to the base 10
† Cytopathogenic effect in tissue culture
†† Mice found paralysed at 10^{-1} dilution
TC = Tissue culture passage
N T = Not tested

new non-hereditary characteristics directly attributable to the cellular ambient in which the agent propagates.[§] Changes in virulence resulting from propagation of the same strain for the same length of time in two different hosts may best be illustrated by the example of the SM (Sickle-Mahoney) strain of type 1 poliomyelitis, which was adapted to mice and cotton-rats in our laboratory, and which undergoes periodic tests in monkeys for paralytogenic properties.[21] Data presented in table VIII indicate that in spite of the similar infectivity end-points in mice and tissue cultures of several substrains of the virus, the virulence of the individual preparations was directly influenced by the species whose tissue was used for the propagation of the virus. The cotton-rat-adapted material was as virulent for rhesus monkeys as the original unadapted strain. In marked contrast, the same virus propagated in either Swiss or PRI mice displayed little or no virulence for monkeys injected intracerebrally. It is interesting to note that spinal-cord tissues obtained from monkeys which show no clinical signs of paralysis seem to be free of histopathological changes, yet preliminary evidence indicates that this apathogenic strain of virus (for monkeys) has lost none of its ability to produce alimentary tract infection.

As far as is known, the stock of attenuated viruses representing types 1 and 2 is today more abundant than that of type 3 variants, but this does not exclude the possibility that mutants of type 3 displaying properties similar to those of the variants of types 1 and 2 will be found in the near future.

Even after modified strains of types 1 and 3 are developed and administered to human subjects, the pathogenic properties of such agents for man will still remain unknown. As mentioned before (page 346), it is not possible to expose great numbers of humans to poliomyelitis in order to obtain statistically significant proof of the safety of a procedure. Moreover, because of the low paralysis-rate of the naturally occurring disease, one may argue that vaccination of ten thousand persons may prove nothing, since (1) no evidence can be furnished as to the susceptibility to infection of the subjects (absence of homologous antibodies), and (2) the ten thousand and first subject may still become a victim of paralysis caused by the so-called attenuated virus.

Under these circumstances, the need is great for specifying other criteria of safety applicable to man himself. Recent studies on viraemia in poliomyelitis[1, 3, 12] impel our thoughts in a certain direction. Would, perhaps, the absence of viraemia after oral administration of the virus to man be considered a valid criterion of attenuation? Although there are still divergent views[1, 10] held on the basic principles of the pathogenesis of

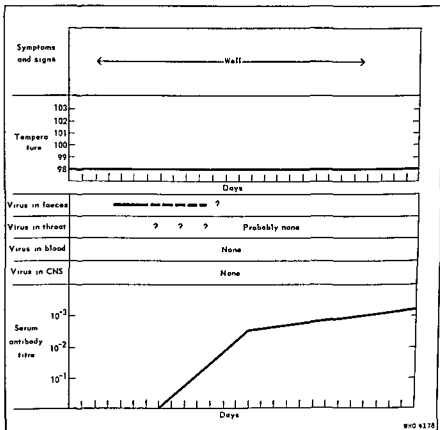
§ This hypothesis is well presented by Luria.[14]

poliomyelitis, the bulk of experimental evidence points to viraemia as an essential phase of infection, *preceding* a possible invasion of the CNS [1, 2, 3, 4, 12] In other words, viraemia was regularly demonstrable in the incubation period after virus feeding to cynomolgus monkeys and chimpanzees, and virus was always isolated from the blood of those animals which subsequently became paralysed [2, 4] Prevention of viraemia and of paralysis by the administration of homologous antiserum to chimpanzees which were fed the virus [4] points again to the blood-stream as the pathway of invasion to the CNS Since antibody response occurred in the alimentary phase of infection and was not conditioned by viraemia, failure to isolate virus from the blood of an individual who developed evidence of intestinal carriage may be considered as an indication of the safety of the immunization procedure

Before considering this point, it is essential to discuss briefly the incidence of viraemia in naturally occurring human infections, and thus to evaluate the statistical significance of the phenomenon In a recent survey,[5, 6] the sera of 84 children who were household contacts of paralytic cases of poliomyelitis were assayed for the presence of the virus Of these 84 subjects, 25 displayed a rise in type 1 antibody between the first and subsequent bleedings 30 days later Moreover, only nine of the 25 children had no homologous antibody at the time of the first bleeding Virus was shown to be present in the sera of five out of these nine subjects. No viraemia was demonstrated by any other individual in this large group of subjects. Four of the five persons who experienced viraemia suffered from symptoms of minor illness, and were febrile at the time of viraemia One was asymptomatic The significant results of this study point to a high incidence of viraemia in natural infections, as evidenced by the fact that five out of nine non-immune subjects developed it

If this be applied to a study of the vaccination of human subjects with living virus, the indiscriminate administration of the virus to thousands upon thousands of individuals does not seem to be the intelligent thing to do. It seems preferable to limit the study, as was done with the TN feeding experiment, to subjects who have no homologous antibodies at the time the virus is administered After feeding of the virus, the blood of the individuals should be submitted to exhaustive examination for its presence, particularly in connexion with positive intestinal carriage If we accept the " viraemia hypothesis ",[1] absence of virus in the sera of a significant number of non-immune intestinal carriers may indicate the inability of a given strain to go beyond the first alimentary phase of human infection and, eo ipso, its relative apathogenicity In view of the high incidence of viraemia (see above) in naturally occurring poliomyelitis infections, the number of subjects used in such a study can be relatively small, yet the results will be of greater significance than would be obtained by vaccinating

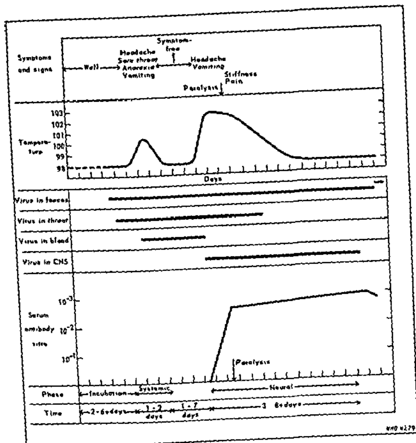
FIG. 1. THE TIME-COURSE OF CLINICAL, PATHOGENETIC, AND IMMUNOGENETIC EVENTS OCCURRING IN AN INFECTION CAUSED BY ORAL ADMINISTRATION OF A LIVING, ATTENUATED VIRUS, OPTIMISTICALLY SCHEMATIZED IN A PARTIALLY SPECULATIVE WAY



thousands of individuals taken at random Thus there is reason to believe that failure to demonstrate virus in the blood of 66 non-immune individuals (see table III) who became infected in an asymptomatic way after being fed the TN strain [19] is a strong argument for the attenuated properties of this strain Fig. 1 presents a chart summarizing clinical and laboratory data obtained in imaginary subjects, immunized, as was the above group, through oral administration of a living attenuated poliomyelitis virus The data are " optimistically " schematized in contrast to those presented by D Bodian [1] (see fig 2) as occurring in a " natural " infection with a virulent strain of virus

Alimentary infection with the virus raises, on the other hand, another problem of safety, namely, the transmissibility of the infection and the

FIG. 2. THE TIME-COURSE OF CLINICAL, PATHOGENETIC, AND IMMUNOGENETIC EVENTS OCCURRING IN "NATURAL" PARALYTIC INFECTION



After Bodian [1] by kind permission of the editors of the *American Journal of Hygiene*

fixation of the modified characteristics of the strain In other words, does a virus lose, in the process of modification, its ability to spread by contagion from one individual to another? Or, if it does retain the ability to spread, might it ultimately regain pathogenic properties? Obviously, the answer to these questions can only come through experience However, once the virulence of a virus is modified, other characteristics may also undergo profound changes For instance, the virulent hog cholera virus present in the excreta of an infected animal is extremely infectious,[11] yet

the attenuated *strain, modified by numerous rabbit passages, causes in* vaccinated animals a self-limited type of infection.[14, 26] Some of the strains of poliomyelitis virus considered suitable for administration to man may have similar properties, and one can envisage an actual clinical trial in a group of non-immune individuals of whom only one would receive the virus by the oral route The entire group, kept in close contact for a time extending beyond the period of alimentary carriage of the virus-fed individual, could be frequently examined for signs of infection, i e , presence of virus in stools and/or development of homologous antibodies. Results indicating low transmissibility would not come as a surprise On the other hand, the concentration of the virus in faecal excreta may also be a factor in determining its transmissibility to other susceptible individuals of the same species One may speculate whether, in such a case, the virus content of the inoculum could be decreased to the point where it would cause no intestinal carriage but would still be sufficient to elicit antibody response Data obtained with the TN strain seem to support the above hypothesis, since a certain proportion of the immunized subjects seemed to remain, within the limits of the experimental procedure, carrier-free

Finally, consideration may be given to the possible suppression of intestinal carriage by the administration of antiviral substances, but experimental data available thus far are not very encouraging, chiefly because of the toxicity of the only known compound which has been employed, to date, for such purposes.[29]

Conclusion

"Fata viam invenient "
Seneca, after Stokes

In this abbreviated account, I have considered it unwise to extol the advantages of immunization with living virus over any other method of vaccination, since scientific data speak for themselves. I have tried to show—*and hope I have succeeded—that the first trial of successful immunization* of man against poliomyelitis with the TN strain of virus warrants additional trials to obtain evidence on the use of other live virus strains which would meet the objections of the most severe critics of such procedures of immunization. Such evidence, coming as it would from unbiased scientific observers, may shift the onus of proof of the undesirability of live-virus vaccination from the present defendants onto the complainants. If that time does come, one will be able to say, contrary to Madame de Sévigné: " Fortune is *not* always on the side of the biggest battalions".

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PASSIVE IMMUNIZATION AGAINST POLIOMYELITIS *

W. McD HAMMON, M D., Dr.P.H.

Professor of Epidemiology, and Head,
Department of Epidemiology and Microbiology,
Graduate School of Public Health, University of Pittsburgh, USA

Background and Literature

When it became reasonably certain to epidemiologists that the control of poliomyelitis by breaking the infection chain was highly improbable, thoughts naturally turned to possibilities of immunization Because of numerous and obvious difficulties existing until the last few years, there appeared to be little hope of large-scale active immunization; hence, it was conceivable that passive immunization might be more practicable at an earlier date. However, even this procedure presented many obvious difficulties

Several uncontrolled tests of passive prophylaxis were made during epidemic times, using either whole blood from adults, or serum from adults or convalescents [11 13 25, 28, 31] No conclusions could be drawn from these trials After gamma globulin was successfully extracted from plasma [8–10] and became available for measles prophylaxis through the American National Red Cross,[26] it was shown in the laboratory to be capable of protecting rodents against an intracerebral injection of the Lansing strain of poliomyelitis,[30] now known as type 2, but at that time not recognized as antigenically different from any other strain Eventually, after determination of three antigenic types, one lot of Red Cross gamma globulin was demonstrated to contain antibody to all three types [3] This fulfilled expectations, since the Red Cross gamma globulin was prepared from a plasma pool of between 50,000 and 100,000 adult volunteers from many widespread geographic areas, and a high proportion of these adults could be expected to have antibody for one or more virus types Such a pool, it seemed probable, would contain all types of antibody in its gamma globulin fraction Moreover, any pool of such a size might be expected to be essentially comparable in antibody titre with any other pool of equal size, provided that extraction methods were standardized.

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*An additional advantage of gamma globulin was its approximately twenty-*fold concentration of antibody as compared with that of the plasma from which it was prepared. Gamma globulin thus appeared to be the agent of choice for any attempted human prophylaxis. In the meantime, a report on limited, but uncontrolled, use of gamma globulin in case contacts was made from Texas [2]

Tests in monkeys with infection produced by injection through the intracerebral,[29] intranasal, or intramuscular routes [4] or by feeding virus immediately after tonsillectomy [1] indicated that protection occurred only when dosages of gamma globulin by weight of monkey were far in excess of anything that would be practicable or even possible in man It seemed probable, however, that human prophylaxis might not require comparable doses, *since the balance between harmless infection and paralytic disease* was usually already weighted by natural phenomenon in favour of man, and the natural route of infection probably represented a less severe challenge

Controlled Field-Trial of Gamma Globulin

Based on the available immunological information on gamma globulin, a voluntary large-scale controlled human test was planned.[18] No conclusions as to possible effectiveness were warranted in advance In three epidemics in 1951 and 1952 [19] about 55,000 children ranging in age from 1 through 11 years were injected, half the number with 0 14 ml of gamma globulin per pound (0 31 ml per kg) body-weight and half with an equal amount of a dilute gelatin solution which resembled the antibody prepa-

occurring in these communities within the age-group of the injected *After 14 weeks of follow-up, and after all decisions had been taken* regarding diagnosis and the degree of final muscle involvement based on a carefully-made muscle analysis 60 days after onset, the type of inoculum was related to the individual patient Prior to this, in order to eliminate the possibility of bias, the inoculum given to any child was not known to anyone participating in the study.

In the analysis,[20, 21] *the incidence-rates of* paralytic disease and the degree of severity of paralysis were compared for all three groups Incidence-rates were entirely comparable in the gelatin-inoculated and in the uninoculated children, but were very significantly lower in the group receiving gamma globulin. When the data were examined by time intervals, little reduction in morbidity was observed in those with onset of the disease

within a week after receiving gamma globulin, though the severity of paralysis was observed to be less During the next four weeks, however, a marked reduction was observed in morbidity, during the subsequent four or five weeks this became rapidly less apparent, and by 10 weeks after injection, rates were again similar in both injected groups No modification of severity could be noted among those in the gamma-globulin injected group who did become paralysed, except in those with onsets during the first week after injection

From this controlled field experiment it was concluded[21] that during a limited period of time after the injection of 0 14 ml of gamma globulin per pound (0 31 ml per kg) body-weight, a child exposed to poliomyelitis had a markedly improved chance of not developing the paralytic disease. Repetition of this would be entirely dependent, of course, on the gamma globulin used having an antibody titre against the virus involved, equal to, or greater than, that of the average present in the product used in the field test Samples of a number of those lots employed have subsequently been tested for all three antibody types by Youngner,[34] using the tissue-culture method, and their titres, as expected, do not show variations which are much greater than those to be expected from the known limits of accuracy of the test method. The potency of other products made from smaller pools and from other geographic areas might differ considerably, however, and lots having a titre 50% lower, which would not be detected with certainty by the tests now in use, might be expected to afford a much shorter period of protection or none at all in the dosage used in this field trial. It has been demonstrated that in children of the age-group most frequently acquiring poliomyelitis, the half-life of gamma globulin is about 21 days[12] The period of significant protection observed, therefore, is only slightly longer than that time in which one-half of the inoculated antibody is destroyed Doubling the dosage, or using a product twice as high in antibody content, would be expected to prolong the period of protection by about 21 days

From specimens of serum and faeces collected from patients and their contacts, in the course of the field trials, an attempt was made to determine whether gamma globulin interfered with infection, as demonstrated by serological tests and tests for virus Another object of these tests was to determine the types of virus present in the outbreaks where the tests were made These laboratory tests were made in part by Dr Cornell and Dr McAllister at the Children's Hospital in Philadelphia, and by Dr. Ludwig and Miss Sather in our department Not all tests have been completed but certain [illegible]

typ [illegible]

2 [illegible]

or type 3 strains have been isolated.

Siblings who were contacts of cases and who had been previously injected with either gamma globulin or gelatin, or who were not injected, excreted detectable amounts of virus in equal proportion Complement-fixation and neutralization tests have not been completed in adequate numbers to make a significant comparison, but at this time there appear to be no conspicuous differences in the final serological response.

It is tentatively concluded from this that gamma globulin in the dosage used has not interfered with infection, the carrier state, or the development of active immunity in the children subsequently exposed to intimate familial contact with a recognized case The only demonstrated effect has been protection of some against involvement of the central nervous system (CNS) of such a degree as may be required to manifest recognizable paralytic involvement Thus, passive-active immunization seems to have occurred

Concurrent and Subsequent Support by Animal Experiments

While the field tests described above were in progress, other related and confirmatory findings were reported from animal experiments In our laboratory [17] protection against paralysis was demonstrated in suckling mice by an even smaller amount of gamma globulin (0 05 ml per pound *(0 11 ml per kg) body-weight) than used in the field trials A type 2 virus* (MEF-1) was employed, which had been adapted to produce disease by intraperitoneal injection [16] It was found that a larger dose of gamma globulin (0 1 ml per pound (0 22 ml per kg) body-weight) did not interfere with infection and the subsequent development of active immunity, even though it protected against paralysis [17] Shortly after this report, Bodian [6] showed that with the Mahoney virus strain (type 1) which had the peculiar capacity of readily producing paralytic disease after heavy and repeated oral feeding in cynomolgus monkeys, a 0 1 ml per kg body-weight dose of gamma globulin would afford protection against paralysis, but not against infection Both Horstmann [22] and Bodian,[5] then, using the cynomolgus monkey and chimpanzees, and virus strains effective by the oral route, were able to detect viraemia in some animals before manifestations of clinical disease However, in Bodian's series it was present only in animals with subsequent paralysis or nervous-system involvement, and although it occurred in five non-paralytic infections of Horstmann, no studies were made to rule out lesions of the cord or brain They postulated viraemia as the method of invasion of the CNS; the viraemia, it was assumed, resulted from a primary intestinal infection. Bodian [5] and Horstmann [23] put forward the thesis that antibody in the blood of man does not prevent the intestinal infection but, by preventing or overcoming

viraemia, protects against involvement of the nervous system Subsequently, a diligent search was made by several investigators [7, 24] for viraemia in contacts of poliomyelitis cases A few virus isolations were made, but in none of these did paralytic manifestations follow.

We felt at this time that it was important to look for viraemia in the suckling mice that were similarly so readily protected by small amounts of antibody, without prevention of infection We therefore tested suckling mice (which were given no gamma globulin) at frequent intervals after inoculation of virus and found no evidence of viraemia at any time before development of paralytic disease (Hammon and associates, unpublished data) We are forced, therefore, to conclude that in this experimental host protection does not necessarily occur at the level of the blood-stream and the CNS by prevention of viraemia

Bodian's and Horstmann's hypothesis of the pathogenesis of human poliomyelitis, based largely on the experimental infection of cynomolgus monkeys and chimpanzees, is of considerable interest, since it also would afford a possible explanation of the mode of action of passive prophylaxis However, in view of the equal effectiveness of gamma globulin in mice, where viraemia cannot be demonstrated, and since it has yet to be established definitely that invasion of the human CNS is normally dependent upon viraemia, no firm conclusions regarding viraemia and the mechanism of passive protection in man can be drawn at present

Application to Possible Effectiveness of Active Immunization

The same hypotheses have been advanced in predicting the possible effectiveness of active immunization However, instead of examining active immunization from such a theoretical approach, based on its possible mode of action, we may now consider it from the standpoint of the demonstrated effectiveness of passively administered antibody in man It can be safely assumed from general immunological principles that if antibody of a specified level will prevent disease when passively administered, the same level of similar antibody acquired actively through vaccination or disease will protect at least as well, if not better Better protection might occur if cellular immunity has also developed in response to the presence of the antigen, and even though immunity is entirely dependent upon antibody, a rapid secondary type of response after infection might provide the necessary antibody even when the level obtained originally from vaccination had fallen greatly

The antibody level in the blood-stream of man from the injection of 0 14 ml of gamma globulin per pound (0 31 ml per kg) body-weight is exceedingly low Calculating its dilution in the total plasma volume,

it can be estimated that if the antibody were all present in the blood at any one time it should be at a level barely detectable by the most sensitive tests currently available Wood and his associates[23] made such tests for type 2 antibody in persons free from detectable type 2 antibody before injection with gamma globulin. He injected from 0.1 ml to 0 4 ml per pound (0.22-0.88 ml per kg) body-weight, and even during the first week after injection was not able definitely to detect the antibody in all persons; when detectable, it was at a minimal level. This is in marked contrast to the levels found necessary from earlier work with vaccines in monkeys, challenged by the intracerebral route It was then shown that a very high blood-level was essential, detectable in a 1/1,000 dilution, a level at which antibody could usually be detected in the spinal fluid[27] Essential levels in man had been postulated by many to be similar. Obviously, a much lower level is adequate in man on the basis of the results of the controlled human gamma-globulin field tests.[21]

However, although I have earlier expressed myself to the contrary,[31] I do not believe at present that it is necessarily true that *any detectable* level of antibody produced by one strain of virus representing each of the three types will protect against *any* poliomyelitis virus encountered in nature, even though that virus may be classifiable as belonging to types 1, 2, or 3 If minor or major type-variation occurs among strains, as present evidence suggests, a very high titre against the strain used as a vaccine might give a very low-protection titre against another strain of the same type Influenza virus would be an extreme illustration of this. It must be pointed out, in respect to American Red Cross gamma globulin used in the field trials, that the large pools of plasma from which it was derived did not merely contain antibodies from just one strain for each type, but represented experience with 50,000 or more persons over many years and in many areas. The protective titre of such gamma globulin can be shown to be high to many different strains of each type This same property of breadth of protection has not been demonstrated yet for the specific antibody response in man immunized against a single virus strain It is this consideration of possible type variation which leads me to retract my earlier statement that if a vaccine produces detectable antibody to each of the three types, it can be expected to protect in general use and would need no field trial Until complete uniformity of strains has been demonstrated, it would appear wise to anticipate that antibody against any one strain of each virus type will not necessarily protect against any other strain in the same way as a similar titre of antibody resulting from the injection of a satisfactory preparation of gamma globulin. Thus, it may be concluded that a low level of broad-spectrum antibody resulting from gamma globulin may be more effective than a similar or even higher level resulting from active immunization with one strain of each recognized type.

Standardization of Gamma Globulin

Now that suitable techniques have been worked out for comparative titrations, any lot of gamma globulin, before use, should be compared by titration with the standard (lot 116-1) used by Youngner,[34] or with a lot used in the field test The appropriate equivalent dosage may then be determined for that lot. Small lots would be expensive to standardize in this manner

Possible Substitutes for Gamma Globulin

Because of the limited availability of gamma globulin in many parts of the world, many substitutes have been suggested Each of these appears to be less desirable to use Any human serum which has not been chemically fractionated in a manner parallel to that used for the separation of gamma globulin, as prepared for the American Red Cross (alcohol precipitation), may contain homologous serum-hepatitis virus Convalescent serum or adult serum, unpooled, or from a small pool, may completely lack the antibody for one or two types of virus, and the antibody which is present may represent a response to only a single strain The titre of any such serum or pool is generally unknown, and no valid estimate can be made of the dosage needed Hyperimmune animal serum or gamma globulin prepared from such serum has the attendant risk of sensitization and reaction common to foreign proteins Thus, there appears to be no entirely adequate substitute for human gamma globulin obtained from very large placental-extract or serum-pools

Limitations in Practical Use of Gamma Globulin

General considerations

In considering the use of gamma globulin in the practice of preventive medicine, many of its limitations readily become apparent, and have been pointed out by us repeatedly [12, 15, 21] Some of these are due to inherent characteristics of the disease, some to the lack of inexpensive and readily-available immunological tests, some to the gamma globulin itself, and others to the general drawbacks of passive prophylaxis

We will discuss first the problem related to individual prophylaxis. Most children need no assistance by artificial immunization of any type to protect them against paralytic poliomyelitis, only a small proportion, which, unfortunately, cannot be preselected, needs it. Among those not requiring protection are children who have already acquired natural, active

immunity through previous mild disease or inapparent infection, and thus may have more antibody than will be given them by injection; others, without specific immunity, would undergo an inapparent or nonparalytic type of infection without artificial immunization. None of these can be readily excluded from any programme. Thus, immunization of any type must be applied to thousands to protect a very few who actually need it.

The time and place of exposure in poliomyelitis is seldom recognized, so that an agent which will afford protection for only slightly over a month may be given too long before exposure occurs or even after exposure. Then again, there may be no subsequent exposure. Thus, the use of gamma globulin is an extremely wasteful procedure, a "shot in the dark" In respect to other persons who may come into contact with the child who is passively protected and subsequently exposed to infection, there are no data to suggest that they would profit in any way unless also injected, since the passively protected child does become infected and does excrete virus following exposure No quantitative data on excretion are available yet, however, so that the possibility of reduced excretion cannot be entirely ruled out

Use in mass prophylaxis

Mass prophylaxis during an epidemic also has marked limitations in effectiveness. The number of cases prevented will be in direct proportion to the morbidity-rate that would have occurred in the age-group inoculated during the short period of effective protection In an outbreak of low intensity, few will be protected per thousand injections given, since the exposure risk is low. Also, if the injections are not given until after the peak of the epidemic is reached the effectiveness will be limited, since, again, the risk is less than it was a few weeks before. Maximal effectiveness will occur during the most severe outbreaks, when the agent is administered so that the peak occurrence of disease would have been at the mid-period of maximal effectiveness of the injected gamma globulin, probably about three weeks after all children were injected. Unfortunately, methods of epidemic prediction are inadequate to permit of selection of the right time and the right place for mass immunization In 1953, when gamma globulin was used for mass prophylaxis in 23 communities in the USA, selected on the basis of what were considered to be suitable criteria, it was given before the apparent peak only once, and in over 50% of the outbreaks it was administered just as the epidemic appears to have terminated spontaneously Many of the outbreaks failed to attain the estimated intensity, and some could hardly be considered as qualifying as epidemics of even minor significance.

It had been anticipated by many physicians and health officers that mass inoculation might stop an epidemic or affect the epidemic curve in

a dramatic way Neither should be expected If the inoculation is made at a time suitable for greatest effect, the period of protection will usually pass well before the end of the outbreak and there could be no interference with the continuation, even in the inoculated population group, without again inoculating all children When only the children up to a certain age are inoculated, the epidemic curve is not dramatically affected, for cases continue to occur in the uninoculated, both children and adults, and some even occur among the inoculated Since excretion of virus does not appear to be curtailed among the exposed, inoculated children, there is no reason to expect reduction of transmission Thus, mass community prophylaxis, in most instances, will actually afford needed protection to a very few and at great expense Those expecting dramatic results may be disappointed, and if the programme is tax-supported the officials responsible may be subject to severe criticism for spending so much money with no measurable or obvious results It was discovered in 1953 that the results of such a programme cannot be measured[32] Results of this type can be assessed only in a controlled test, such as that made in 1951 and 1952

Use in contact prophylaxis

Another suggested field of possible effective application has been passive immunization of family and other intimate contacts of recognized cases of poliomyelitis There is no direct experimental proof of its effectiveness under such circumstances, but on the basis of certain epidemiological and immunological assumptions the method would appear to have reasonable merit

Contact prophylaxis is the basis of most of the use of gamma globulin in measles Shortly after known exposure, frequently from a sibling, the exposed non-immunes are injected A small dose soon after exposure or a larger dose at a slightly later interval affords complete protection, while modification occurs with smaller doses at either interval The dosage required has been determined by use under these exact conditions The problem in poliomyelitis, however, is quite different First of all, susceptibles cannot be determined on the basis of a history of no previous attack, so all, up to some arbitrary age, must be presumed susceptible, though many are not This means waste The incubation period and the period of infectiousness in poliomyelitis are much more variable than in measles, so that time relationships in the incubation period are less readily determined Even more important is the difference in the temporal distribution of subsequent cases in a family after the index case In measles the index case is most frequently the primary family infection, and subsequent cases are true secondary infections following about 12 days later. In poliomyelitis it seems probable, from all available information, that the

index case is seldom the primary family infection, and most subsequent cases are infected simultaneously with the index case, all probably having been exposed earlier to another member of the family or to a visitor who failed to develop an illness which could be diagnosed as poliomyelitis. It has been observed repeatedly that about 60% of all cases occurring after the index case have their onsets within a period of five or six days after that of the index case, 30% in the next seven days, and only 10% more than 12 days later These latter may be infections actually acquired from the index case. Furthermore, it should be pointed out that the dosage of gamma globulin determined by experimental methods in the controlled mass field-trials might apply in large part or entirely to the requirements if given before infection, rather than after infection, while when dealing with family contacts almost all who will be infected are presumably already infected when the injection is made. Under such circumstances a larger dosage might be required, only a controlled experiment can determine this.

At first glance, on the basis of the above considerations and the usual concept of low attack-rates for multiple family cases, it would appear that this was not a suitable field for gamma-globulin use However, there are theoretical points in its favour When the family populations are enumerated in all families where a single case of poliomyelitis is diagnosed, and a morbidity-rate is calculated for all subsequent cases, these rates are extremely high as compared with the general population For example, from the records of 475 families with one case, with 1,512 exposed family members in two of the areas in the field trials of 1951 and 1952 (Utah and Iowa-Nebraska), there were 51 subsequent cases in these same families The rate of subsequent cases for all ages was thus 3,373 per 100,000 In the age-group 0-15 years, with 41 cases, the rate was 6,175 If these rates are reduced to 10% to apply only to cases occurring more than 11 or 12 days after the index case, they are 373 and 617 per 100,000, for all ages and for the 0-15 age-group, respectively These late cases are presumably secondary to the index case, and comparable to secondary measles cases Most of these will occur within a period between the second and third week after gamma globulin might be given, and rates as high as these in any similarly short period of time, before which gamma globulin might be used in mass prophylaxis in the general population, appear under exceedingly rare conditions Thus, *if* gamma globulin will prevent a high proportion of the late subsequent family cases, this would appear to be the most effective use to which it could be put in terms of cases prevented per thousand doses used.

In addition to the possible benefits just outlined, if gamma globulin has any preventive effect, or, as seems more likely, a modifying effect, when given less than one week before onset, another 30% of subsequent cases (onset 5-12 days after the index case) may be benefited to some degree.

Experimental information on this point is even more tenuous, although it appears from the controlled field trials that modification of severity of paralysis might have occurred in those persons with onset less than one week after injection. It is not known, however, whether these persons in the field trials were injected before or after exposure, since it is believed that the incubation period may be less than 7 days in some instances. Subsequent cases in a family, however, with onsets within 5-12 days of that of the index case, can, with considerable assurance, be assumed to have been infected when the index case is diagnosed

The whole problem of family-contact use of gamma globulin, therefore, rests on whether or not gamma globulin will protect or modify the disease if given after infection, and if so, what the necessary dosage is under such circumstances The answer to this is not known, but we are inclined to expect behaviour parallel to that in measles and hepatitis We suggest empirically that the dosage be doubled in post-infection usage until better information becomes available

In the 1953 outbreak in the USA, an attempt was made to analyse the results of this type of usage, with a dose of 0 14 ml per pound (0 31 ml per kg), body-weight [22] In my opinion, the data collected do not permit of a satisfactory analysis [32] Furthermore, the potency of the lots of gamma globulin used could certainly influence the results In this respect, the potency of the specific lots used has not been examined in relation to families which did or did not have cases Many of the lots used were *not* from extremely large pools of plasma This problem is therefore unsolved, and requires further study in adequately controlled tests with gamma globulin of known titre

Other special circumstances

Outbreaks of poliomyelitis in summer camps and boarding schools have occasionally led to very high morbidity-rates and the use of gamma globulin to prevent this must be considered This situation may be analogous to an outbreak in a larger community or, again, to multiple cases in a family Nevertheless, what may happen after a single case, or even after several cases, is unpredictable However, the potential danger to the rest of a group living under such conditions of intimate exposure is so great, and the responsibility that must be borne by those in charge is so unenviable, that it would appear that this might be one of the most striking applications for attempted passive prophylaxis of the child population concerned

Another proposed use for the agent is administration to a child who is to undergo a tonsillectomy during the poliomyelitis season It appears most probable that post-tonsillectomy poliomyelitis, the bulbar type with

onset 7-18 days after the operation, occurs as a result of infection already incurred before tonsillectomy The trauma may permit of direct invasion of exposed nerve fibres by virus already present in the throat. The experimental work of Adams and his co-workers[1] with cynomolgus monkeys which were tonsillectomized and then immediately fed virus showed that very large doses of gamma globulin were required to prevent the disease and it had to be administered before the virus. In this instance the experimental disease may have a close parallel to the human surgical experience and the dose of gamma globulin that would be required to prevent direct invasion of nerves from a wound might be inordinately large. With no other source of available information, it appears reasonable to predict little effectiveness unless doses of 1-2 ml per kg body-weight were administered before tonsillectomy. Since this is entirely impracticable, and even then of questionable value, it is certainly not a means to employ to offset the generally accepted hazards of routine tonsillectomies during poliomyelitis outbreaks

Conclusion

The demonstration of the effectiveness of a very low level of antibody in preventing paralytic poliomyelitis in man without preventing infection and the subsequent development of active immunity, probably has its greatest importance in changing concepts previously held in respect to the possible effectiveness of active immunization with killed virus. However, *it remains to be shown that a similar or even higher level of antibody* resulting from vaccination with a single strain of virus representing each of the three known types will be as effective as the broad-spectrum antibody found in gamma globulin.

Although gamma globulin has been shown to be effective in the controlled field trials, the dosage factor is of great importance Titration of potency of each lot in comparison with a standard to determine the dosage required is essential

There appears to be no suitable substitute for gamma globulin, either in the form of convalescent or adult human serum, or gamma globulin from hyperimmune animals

Gamma globulin, although demonstrated to have temporary preventive effects in poliomyelitis under certain conditions, has a very limited field of wide-scale application *It would seem reasonable to conclude that among* tax-supported public-health measures in most parts of the world it would not compete favourably in respect to accomplishments versus cost-ratio with most other approved programmes, and therefore cannot be recommended.

Undoubtedly, however, there are certain limited circumstances in which its use would be indicated. Those might include some institutional or summer-camp groups, after a case has been recognized.

If, however, the cost of the gamma globulin is borne by a voluntary health organization, or by the consumer, and it is available in adequate quantity and known potency, the problem is quite different Administration then might be by a health department at a minimal expenditure of tax-revenue, or by private physicians on a fee basis. Under such circumstances, where desired by the public, as expressed by contributions to the voluntary organization or by request to a private physician, mass immunization at suitable times and places can be expected to serve a useful purpose Cost per case prevented, though large, is still probably less than would be the cost of care through normal life-expectancy of the persons who would otherwise be crippled to the degree requiring complete support. The psychological trauma of residual paralytic disease, both to patients and to their families, cannot be measured in money, and this also is prevented to the same degree Furthermore, where gamma globulin is desired by parents for children shortly after reasonable evidence of exposure, and is [illegible]
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if or where it can be afforded Protection under these circumstances, however, has not been proved, and sharply differing opinions are held

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PUBLIC-HEALTH MEASURES IN THE CONTROL OF POLIOMYELITIS

A M.-M. PAYNE, M D., M R C P.

Division of Communicable Disease Services, World Health Organization

In 1891, Medin[46] described the Stockholm poliomyelitis epidemic of 1887, but at first little attention seems to have been paid by public-health authorities to the possibility that poliomyelitis was an infectious disease. In 1907, Wickman[66] clearly stated that poliomyelitis was a contagious disease spread both by typical and abortive cases and by healthy carriers Landsteiner,[40] by transmitting the disease to monkeys, proved its infective nature conclusively, and from then onwards publications urging public-health measures to control the disease began to appear with increasing frequency Flexner[25] advocated quarantine measures which should include both the patient and his attendants, on the grounds that the disease was spread by healthy carriers He regarded a quarantine period of from three to four weeks as necessary, and emphasized the importance of the safe disposal of nasal, buccal, and other excretions He also suggested the possibility that flies might be important in the spread of the disease In the years which followed, numerous publications re-emphasized and expanded these recommendations to include notification of the disease, quarantine of the family, placarding, fumigation, investigations into milk-, water-, and food-supplies to ensure their safety, prohibition of public gatherings, especially of children, postponement of the opening of schools, and restriction of movement into and out of an infected area [1, 21, 28, 48] Such measures were more or less strictly applied until about two decades ago There was little or no objective information on the results achieved which would enable an assessment to be made of their value in a given epidemic Indeed, the general verdict of health officers was that the measures were of very little value, since epidemics of poliomyelitis became more common and more extensive, and in a given epidemic it was not possible to demonstrate that they had had an [illegible]

to the fact that poliomyelitis is an infectious disease. It is true that there have been reports of encouraging results in small outbreaks,[23] but generally most health officers have had little faith in the value of general public-

However, there is evidence on which working hypotheses may be based. Epidemics appeared after the role of defective sanitation in the spread of intestinal infections began to be appreciated, and they occurred first in those countries in which the new ideas were being most rapidly and effectively applied, that is to say, in those countries in which standards of living were being rapidly improved and in which, as a result, many changes in the pattern of social behaviour were taking place. As other countries have attained similar standards so they too have suffered epidemics of increasing severity. In parallel with this change in the incidence of disease there has been a change in the age-groups predominantly affected; this was observed first in North America, Scandinavia, and Australia, the same regions which first experienced poliomyelitis in epidemic form,[17, 22, 45, 49] the tendency being for paralytic poliomyelitis to appear in progressively older children, adolescents, and even adults. An interpretation of these observations is that poliomyelitis infection is spread in a way that is *restricted by the hygienic measures and the changes in social behaviour* associated with the attainment of higher living standards, but it is not eliminated, so that primary infection is often merely delayed until an age *when the results of infection tend to be more severe and hence more often* recognized. There is now a considerable body of evidence to suggest that this interpretation is at least partially correct, although it is difficult to explain all observed facts in this way alone. (These facts are reviewed in other articles in this monograph, notably those by Paul, Gear, and Sabin (see pages 9, 31, and 297), and the appropriate references may be found therein.)

There is yet another explanation, which may also be true since the two explanations are not mutually exclusive (see particularly the article by Sabin), that is that the poliomyelitis viruses may undergo changes which render them more liable to invade the central nervous system and cause paralysis. By analogy with the behaviour of other viruses, such changes would presumably involve mutation. This may have occurred once only, the mutant having been spread elsewhere by man, or, perhaps more probably, mutation may take place from time to time in a number of different places. In the latter event, the varying intensity and severity of epidemics may be connected with several possible mutations associated with various changes in the characteristics of the virus. At present, this explanation must be regarded as tentative, although there is good evidence *to establish mutability of virulence of the poliomyelitis viruses in the* laboratory, and Sabin & Steigman[59] have produced epidemiological evidence in its favour. However, it certainly provides a possible explanation of epidemics difficult to explain otherwise.[b]

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[b] For example, the 1947 outbreak in Great Britain was at the time by far the most severe ever recorded there, and it cannot easily be explained in terms of any recent change in the host or in the environment.

health measures in poliomyelitis control, although they might apply them for the important purpose of allaying public anxiety

A great deal of new information has come to light in recent years, and it may be as well to re-examine the place of public-health measures in the control of poliomyelitis in terms of current thought on the epidemiology of the disease

Important though the advances in knowledge are, there are still many points which remain obscure or unproven. It may therefore be permissible to indulge in some speculation when these uncertainties affect the possible application of public-health measures

THE EPIDEMIOLOGY OF POLIOMYELITIS AS IT INFLUENCES THE APPLICATION OF CONTROL MEASURES

The only manifestation of infection with poliomyelitis virus which causes concern is the occurrence of clinical symptoms—particularly paralysis—due to involvement of the central nervous system If symptomless alimentary infection, or even the minor illness, were the only results of infection, the virus would still be of interest to the epidemiologist but it would have no public-health importance The history of poliomyelitis suggests that in the first half of the 19th century the clinical disease was rare and largely restricted to infants, while epidemics were almost unknown However, towards the end of the century—perhaps, as suggested by Burnet,[18] the Stockholm epidemic of 1887 may be taken as the beginning of this phase—a change became evident epidemics began to appear, and have irregularly occurred since on an increasing scale in more and more countries [10, 62, a] There are now few countries in the world which have not experienced an outbreak at least as large as the 1887 Stockholm epidemic The phrase "the incoming tide of poliomyelitis" used by Stowman [62] gives an admirable picture of the situation the shore is being increasingly covered and the waves are growing larger If the tide were to change and recede to its position before 1887, there would be little need for action by health authorities

Some Theories Regarding the Causes of the Changes in the Behaviour of Poliomyelitis

The reasons for the progressive change in the behaviour of poliomyelitis since the end of the 19th century cannot yet be said to be fully understood

a See also the articles by Paul and by Freyche & Nielsen on pages 9 and 59 of this monograph.

host but clinical symptoms develop rarely or not at all. A more conventional approach would be aimed at reducing the amount of infection in the environment This approach has been practised in the past, as already indicated, and although the general opinion has been that it has been ineffective, in fact it seems to have achieved a limited measure of success.

continuously applied in well-developed countries. In these countries, which have high standards of living and good hygiene conditions, the results of serological and virological examinations suggest that there is now less poliomyelitis infection than in countries where conditions are more primitive. Unfortunately, although there may be less infection there is more clinical disease, so that as far as poliomyelitis is concerned hygienic measures seem to have done more harm than good

The Influence of Social Factors

It is, however, by no means certain that improvements in sanitation and hygiene are wholly responsible for this change There are other factors to be considered involving changes in the biological environment of the infecting agent brought about by changes in social behaviour For example, if, as is quite possible, or even probable,[14 17 27] poliomyelitis infection is predominantly transmitted during personal contacts between children, especially in areas where spread resulting from defective sanitation is reduced, then the age at which the maximum number of infections would occur would be expected to depend on the age at which the number and intensity of such contacts between children were sufficient to make exposure probable In communities with well-developed social systems of the type associated with Western civilization, families tend to be smaller and external contacts between young children tend to be fewer and more closely supervised than under some other social systems or in less well-developed communities, particularly where there is overcrowding The number of opportunities for exposure to infection is thus reduced until school age is reached. This hypothesis is supported by the observation that in rural areas, where the dispersed population reduces the frequency of child-to-child contacts, poliomyelitis tends to attack children who are older than those infected in urban areas, where there is overcrowding[49] It might therefore offer an additional explanation of the present tendency, observed particularly in countries with the Western type of social system, for school-age groups to be most seriously affected, and since poliomyelitis infection produces clinical disease both more frequently and of a more serious nature in older

A change in the neurotropic properties of the virus might occur within the country involved, or the virus might be imported from another country where its altered properties need not necessarily have been apparent should the state of immunity of the population have been sufficiently high. Much research is needed before this explanation can be fully accepted, and success will depend on the development of techniques for the detection of such strain differences in the virus

Control of the Primary Infecting Agent

The importance of solving this problem is obvious If changes in the inherent properties of the virus have not occurred in nature, then it might theoretically be possible to change the calendar back to the early 19th century by ensuring that all infants received orally a small dose of unattenuated living virus,[c] and by ensuring that the virus was so widely spread that no one would escape early primary infection and repeated reinforcing infections Some infants would undoubtedly develop paralysis, as they did in the 19th century, and deaths would occur, but the overall incidence of both paralysis and death would presumably be considerably reduced in comparison with present figures However, such empirical methods cannot seriously be considered today

If, on the other hand, changes in the inherent qualities of the virus have occurred under natural conditions, then it should be possible to induce them in the laboratory and to produce an avirulent virus Recently, considerable progress on these lines has been made (see the articles by Sabin and Koprowski, pages 297 and 335) With strains of avirulent virus that retain their immunizing power, the safe reproduction of the natural process of immunization may become possible [d]

Control of Infection in the Environment

The approach to the control of poliomyelitis which has been considered so far is based on the principle of the widest possible distribution of the infecting agent secured in such a way that immunity is produced in the

[c] A degree of protection during the first few months of life is derived from maternal antibodies which were presumably consistently present in the 19th century Similar protection might be ensured today by injection of immune globulin before administration of the virus

In these endemic areas in tropical and subtropical regions, poliomyelitis is, in general, still behaving in the pattern of the 19th century There are only relatively few cases of clinical disease among very young children, and epidemics are rare and small in size when they do occur. Since there are many much more pressing problems in these areas, it is doubtful whether at the present time much effort can or should be expended on the control of poliomyelitis It may nevertheless be anticipated that the situation will change in the future as social and hygienic conditions improve and, as described in the articles by Gear and by Freyche & Nielsen in this monograph (see pages 31 and 59) there are signs that this is already happening in some parts of the world

In epidemic areas the number of inapparent infections, and probably also the proportion of inapparent to overt infections, varies greatly at different times In times of severe epidemics inapparent infections may be numerous During a severe urban epidemic, for example, with an incidence of clinical disease of 100 per 100,000 population, on the basis of a 100 to 1 ratio it is possible that there may be as many as 10,000 inapparent infections per 100,000 population Too much cannot be expected from hygienic measures in such circumstances However, in other circumstances the number of silent infections, and probably the proportion also, may be much less[51, 63] There is increasing evidence that early in an outbreak, in inter-epidemic periods when only isolated cases occur, and even during some outbreaks in highly developed communities, infection may be rather sharply restricted to close associates of clinical cases[15, 16, 26, 47, 52, 53] The proportion of silent infections will be dependent on the number of close associates of each case, and in rural areas and isolated communities, especially, the number is likely to be relatively small Under these circumstances the systematic application of hygienic measures would seem to be more hopeful Thus, while, on the one hand, experience has shown that during extensive epidemics the application of measures such as isolation and quarantine in the area involved does not lead to detectable results, even though presumably a number of infections and some clinical cases are prevented, on the other hand, if such measures were applied early in the poliomyelitis season before an epidemic has developed, both in areas where cases have occurred during inter-epidemic periods and in rural areas among relatively isolated communities, they might be expected to have a real effect on the incidence of the disease during the subsequent epidemic season This may be regarded as a logical extension of the application of general sanitary measures which, as already noted, seem to have reduced the amount of poliomyelitis infection in highly developed communities, even though they have not hitherto been applied specifically against poliomyelitis

children than in infants, an increase in the number of recognized clinical cases would result. Thus delayed primary infection due both to improved hygienic practices and to a reduction in child-to-child contacts in the younger age-groups may act by producing more clinical disease in older age-groups. The change in age structure of the population must, of course, also be taken into account.

It is an alarming thought that while, by improving environmental sanitation and hygiene and raising living standards generally, the health worker has in many parts of the world practically eliminated a number of serious epidemic diseases he may at the same time have created a new one. Of course, the credit balance is strongly in favour of hygienic measures and high living standards, but we cannot be satisfied until we have eliminated any deleterious effects of our interference with natural processes and retained only the benefits. There is a warning here of general application: any large-scale disturbance of the ecology of natural processes may be followed by unexpected, and often undesirable, side effects.

Isolation and Quarantine

However, the adverse effect of hygienic measures on poliomyelitis may well have been partly the result of faulty or incomplete application. A logical consideration of recent advances may enable us to apply them with more hope of success. The relevant facts will be found in other articles in this monograph and in the first report of the WHO Expert Committee on Poliomyelitis,[68] and only a brief summary is needed here.

Poliomyelitis is a highly infectious disease. The virus appears to enter the body by the mouth, either in the course of intimate association with infected persons who are shedding the virus in pharyngeal secretions or in faeces, or as a result of environmental contamination (including food and water) with infective faecal material directly, or indirectly by flies which have fed on contaminated material. The relative importance of these methods of spread evidently depends on the environment. The great majority of infected persons show no clinical evidence of infection. Its presence in them can be detected only by isolation of the virus in the laboratory or, indirectly, by demonstrating a rise in serum antibodies. The ratio of symptomless infected persons to clinically diseased patients varies at different ages[47] and under different circumstances. In epidemic areas, as already indicated, it appears to be less than in endemic areas; a ratio of 100 to 1 has been suggested for the former,[20, 38, 61] while in endemic areas, judging by the early age at which the great majority of children can be shown serologically to have been infected[32, 50, 57, 58] and the comparative rarity of clinical disease, the ratio must be much higher, perhaps 1,000 to 1 or even more.

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In epidemic areas the number of inapparent infections, and probably also the proportion of inapparent to overt infections, varies greatly at different times In times of severe epidemics inapparent infections may be numerous. During a severe urban epidemic, for example, with an incidence of clinical disease of 100 per 100,000 population, on the basis of a 100 to 1 ratio it is possible that there may be as many as 10,000 inapparent infections per 100,000 population Too much cannot be expected from hygienic measures in such circumstances However, in other circumstances the number of silent infections, and probably the proportion also, may be much less [51, 63] There is increasing evidence that early in an outbreak, in inter-epidemic periods when only isolated cases occur, and even during some outbreaks in highly developed communities, infection may be rather sharply restricted to close associates of clinical cases [15, 16 26, 47, 52, 53] The proportion of silent infections will be dependent on the number of close associates of each case, and in rural areas and isolated communities, especially, the number is likely to be relatively small Under these circumstances the systematic application of hygienic measures would seem to be more hopeful Thus, while, on the one hand, experience has shown that during extensive epidemics the application of measures such as isolation and quarantine in the area involved does not lead to detectable results, even though presumably a number of infections and some clinical cases are prevented, on the other hand, if such measures were applied early in the poliomyelitis season before an epidemic has developed, both in areas where cases have occurred during inter-epidemic periods and in rural areas among relatively isolated communities, they might be expected to have a real effect on the incidence of the disease during the subsequent epidemic season This may be regarded as a logical extension of the application of general sanitary measures which, as already noted, seem to have reduced the amount of poliomyelitis infection in highly developed communities, even though they have not hitherto been applied specifically against poliomyelitis

children than in infants, an increase in the number of recognized clinical cases would result Thus delayed primary infection due both to improved hygienic practices and to a reduction in child-to-child contacts in the younger age-groups may act by producing more clinical disease in older age-groups. The change in age structure of the population must, of course, also be taken into account.

It is an alarming thought that while, by improving environmental sanitation and hygiene and raising living standards generally, the health worker has in many parts of the world practically eliminated a number of serious epidemic diseases he may at the same time have created a new one. Of course, the credit balance is strongly in favour of hygienic measures and high living standards, but we cannot be satisfied until we have eliminated any deleterious effects of our interference with natural processes and retained only the benefits There is a warning here of general application any large-scale disturbance of the ecology of natural processes may be followed by unexpected, and often undesirable, side effects.

Isolation and Quarantine

However, the adverse effect of hygienic measures on poliomyelitis may well have been partly the result of faulty or incomplete application A logical consideration of recent advances may enable us to apply them with more hope of success The relevant facts will be found in other articles in this monograph and in the first report of the WHO Expert Committee on Poliomyelitis,[68] and only a brief summary is needed here.

Poliomyelitis is a highly infectious disease The virus appears to enter the body by the mouth, either in the course of intimate association with infected persons who are shedding the virus in pharyngeal secretions or in faeces, or as a result of environmental contamination (including food and water) with infective faecal material directly, or indirectly by flies which have fed on contaminated material The relative importance of these methods of spread evidently depends on the environment. The great majority of infected persons show no clinical evidence of infection. Its presence in them can be detected only by isolation of the virus in the laboratory or, indirectly, by demonstrating a rise in serum antibodies The ratio of symptomless infected persons to clinically diseased patients varies at different ages [47] and under different circumstances. In epidemic areas, as already indicated, it appears to be less than in endemic areas; a ratio of 100 to 1 has been suggested for the former [20, 38, 61] while in endemic areas, judging by the early age at which the great majority of children can be shown serologically to have been infected [32, 50, 57, 58] and the comparative rarity of clinical disease, the ratio must be much higher, perhaps 1,000 to 1 or even more

to a virulent strain or to a strain of an aberrant immunological type might overcome the resistance of a proportion of those persons immunized Also, it is not yet known what effect active immunization will have on the prevalence of the poliomyelitis virus. If as a result the virus has diffi- [illegible] work of Koprow- [illegible] become relatively [illegible] bacillus when the proportion of immunized persons is sufficiently high "Reinforcing" infections would then take place infrequently and, as immunity waned, the population, particularly adults, would once more be in danger, especially from the introduction of virus of high virulence from outside It would therefore seem to be as wise to control subsequent exposures to the virus antigen by the application of hygienic measures and by the administration of reinforcing doses of vaccine as it is to control the primary experience

It is concluded, therefore, that as procedures for active immunization become available, they should be supported by measures designed to reduce the amount of infection in the environment.

The Future Place of the Laboratory in Poliomyelitis Control

The possible value of isolation and quarantine under certain circumstances has already been mentioned, but it is evident that their value would be enormously increased if it were practicable to detect the presence and duration of infection in a given individual This has been technically possible for many years, but the older techniques, based on the isolation of the virus in monkeys, have been too expensive and time-consuming for routine use The developments which have followed the introduction of tissue-culture techniques (see the articles by Enders and by Rhodes et al. (pages 269 and 237), promise to provide a means whereby such routine examinations may become practicable At present, the techniques are hardly sufficiently developed, and it is certain that the number of laboratories with trained staff able to carry them out is totally inadequate to permit of any general application of the procedure However, progress is rapid and it may be anticipated that practical procedures will become available in the near future It is clear that, if they are to be applied, many more laboratories will be needed and many more virologists must be trained Such development of laboratory services will necessarily take a number of years and should therefore be begun without undue delay or the health officer will be unable to take advantage of the new techniques It would seem logical to develop such increased virus laboratory services as part of a public-health laboratory service, especially since the public-

The Essential Role of Active Immunization

However, as has already been pointed out, should these measures be effective, for every clinical case prevented a natural inapparent immunizing infection would also be prevented in a much larger number of other persons Primary infection in these persons would therefore be further delayed and when it did occur—which at present seems almost inevitable—the effects would tend to be more serious. In the absence of specific control measures, such as active immunization, it would seem, therefore, that as far as poliomyelitis is concerned hygienic measures may actually be undesirable—a conclusion already reached on historical grounds.[a]

Furthermore, since there is a possibility that different strains of poliomyelitis vary in their tendency to invade the central nervous system, it would be essential to know in a given epidemic whether or not the responsible virus was particularly neurotropic If it were strongly neurotropic, clearly every effort should be made to restrict its spread. If it were not, a larger number of persons might benefit in the long run (assuming no prospect of artificial immunization) if its spread was unchecked and they were permitted to experience a natural immunizing infection , for if it could be ensured that the inevitable primary infection was with such a strain, a smaller proportion of persons would develop paralysis Unfortunately, there is at present no way of knowing whether or not a given strain is particularly neurotropic The incidence of paralytic cases gives no information on this point without corresponding information being available as to the incidence of inapparent infections There appears to be little reason to assume on epidemiological grounds that neurotropism is necessarily linked with any special tendency of the virus to spread

Fortunately this quandary is to some extent resolved by recent developments in research on artificial immunization in poliomyelitis These are discussed in the articles by Sabin and by Koprowski (see pages 297 and 335) If, as seems probable, a satisfactory method of artificial immunization becomes available, using either an avirulent or an inactivated virus vaccine, hygienic measures to limit the spread of virulent virus would appear to be a necessary part of the control programme It might, of course, be argued that, if immunization is effective, subsequent natural exposures would be advantageous since they would act as reinforcing doses. This might be true in the majority of instances, but heavy exposure

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to a virulent strain or to a strain of an aberrant immunological type might overcome the resistance of a proportion of those persons immunized Also, it is not yet known what effect active immunization will have on the prevalence of the poliomyelitis virus. If as a result the virus has diffi- [illegible] proportion of immunized persons is sufficiently high "Reinforcing" infections would then take place infrequently and, as immunity waned, the population, particularly adults, would once more be in danger, especially from the introduction of virus of high virulence from outside It would therefore seem to be as wise to control subsequent exposures to the virus antigen by the application of hygienic measures and by the administration of reinforcing doses of vaccine as it is to control the primary experience

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health importance of a number of other virus diseases is becoming increasingly apparent as bacterial diseases come under control. Existing research laboratories should not be swamped with routine work for, if they are, progress will cease However, if developments take place as envisaged, it may become as normal and as easy for the health officer of the next generation to trace infection with poliomyelitis virus as it is for him to trace typhoid carriers today.

Control of Non-Specific Factors Influencing the Incidence of Paralysis

The first method of approach to the control of poliomyelitis already discussed is directed essentially towards control of the characteristics of the primary infecting agent—the dissemination of virus of low virulence The second is directed towards a reduction in the amount of natural infection in the environment, accompanied by the production of an active immunity in the host by artificial immunization. There is yet a third method of approach directed entirely towards the host, consisting of the control of factors affecting the susceptibility of the host, other than specific immunity, which alter the frequency or the severity of paralysis following infection

Numerous non-specific factors have been suggested as predisposing to or precipitating paralysis They include age, genetic factors, physique, *endocrinological disturbances, pregnancy, nutrition, other infections*, trauma, tonsillectomy, dental extractions, certain injections, over-exertion, exposure, and exhaustion from various causes The evidence for the part played by some of them is incomplete, the influence of others is well-established The effect of age at the time of infection has already been mentioned There is no longer any doubt that on the average children aged between one and five develop paralysis after infection less frequently and less severely than older children, and that the severity of the disease, particularly the incidence of bulbar poliomyelitis, increases further in adolescence and adult life [41, 47, 49] The position regarding infants under one year of age is less clear In some countries serious disease is being recorded more frequently than formerly in very young babies,[20] an observation which may be related to the fact that a number of mothers in highly developed countries have no antibodies to transmit to their children and possibly to the fact that generally *in these countries a smaller proportion of infants* are breast-fed and for a shorter period; poliomyelitis antibodies can be detected in human milk if they are present in the mother's serum, although their importance is still obscure The change might also be related to an increase in the incidence of infection in adults in these countries, of whom

a smaller proportion are solidly immune. Parents may therefore more often infect their very young children who have few other opportunities for exposure. Apart from the general deductions which have already been drawn from this effect of age at the time of primary infection, these observations make it clear that in highly developed communities it is not justifiable to assume that very young babies are protected by maternal antibodies; the relatively low incidence among them may be more a function of the reduced opportunities for exposure. Furthermore, in these communities adults should not lightly expose themselves to infection, since one in ten or more may still be fully susceptible. That this is a real danger is borne out by the increasing number of both nurses and parents who have been infected and have developed severe paralysis while nursing children who may have suffered only a mild or abortive attack. Since it may be anticipated that the proportion of susceptible adults will tend to increase in the future, it may become necessary to measure the state of immunity of nurses about to undertake the care of poliomyelitis patients, as is often done for tuberculosis and some other infectious diseases.

The possible effect of genetic factors,[6] nutrition, and physique will not be discussed in detail. Genetic factors are beyond the control of the health officer. The possible effect of nutrition is briefly discussed by Gear in his article (see page 31). If there is an effect, it would seem that malnutrition or an unbalanced diet has a favourable effect. However, direct evidence is lacking and there are other more convincing explanations of the observed facts. As far as physique is concerned, the observations of Draper[24] have not been confirmed by others.[42] Other observers have commented on an apparent increase in the severity of paralysis among athletic types. This may, however, be related more to the tendency of such persons to undertake severe exertion (see later paragraphs) than to their physical constitution per se.

The possibility that endocrinological disturbances may affect the incidence of paralysis derives support from laboratory observations that adrenocorticotrophic hormone (ACTH) and cortisone increase the susceptibility of certain laboratory animals.[60] However, apart from endocrinological changes associated with pregnancy and a suggestive rise in the incidence of the disease about the age of puberty, there is little convincing evidence that this happens in man. It is reasonably well established that poliomyelitis may run a severe course during pregnancy.[5, 8, 19, 37, 41] Whether this is due to endocrinological or other changes is not known. There is a difference of opinion as to whether or not the seriousness of the disease varies according to the duration of the pregnancy. There is some evidence[12] that deaths occur most frequently in the last trimester. The foetus is generally not affected, although abortion may occur, and there is evidence that the infant may be infected at or shortly before delivery.

It is clear that care should be taken to reduce the possibility of exposure of pregnant women in epidemic times. Under some circumstances it might be wise to administer a prophylactic dose of gamma globulin.

The role of other infections in predisposing to paralytic poliomyelitis is not well substantiated [39] Such an effect would be difficult to prove, especially since most of the infections which have been incriminated are common diseases of childhood. Association by chance would therefore be expected to occur not infrequently. There is perhaps more evidence incriminating pertussis than most other diseases Nevertheless, on general principles it would seem wise to bear the possibility in mind and to take special care to limit the spread of other infectious diseases when poliomyelitis is epidemic. Another good reason for this is that the early diagnosis of poliomyelitis which is so important may be confused if other diseases are prevalent at the same time

If the word "trauma" is used in a broad sense covering injuries such as a blow, a fall, a fracture, surgical operations, certain injections, and over-exertion, fatigue, and exhaustion, there is no doubt that it has a pronounced effect on the appearance of paralysis following poliomyelitis infection The best and perhaps the most important example of this is that exertion at the time of the major illness, when signs of central-nervous-system involvement have already appeared, may cause very severe and extensive paralysis [36, 56] This is fully discussed in the article by Russell (see page 137), to which reference should be made for further details. The avoidance of this effect is an important public-health measure in poliomyelitis This may be illustrated by the observation that the case-fatality-rate in patients admitted to hospital was nearly three times higher in patients transported long distances—average of 85 miles (135 km)—than in local patients [13] Following infection, the avoidance of all exertion may often make all the difference between a non-paralytic and a paralytic illness, and if central-nervous-system involvement has already occurred, it may be a life-saving measure.

In epidemic times it may be justifiable to apply this principle more widely. In infants the minor illness may escape notice altogether and the first suspicion of illness may be aroused only when the major illness begins Complete rest is then imperative In adolescents and adults a diphasic illness is less common than in children and the onset of the major illness may be more insidious [35] Such patients often fight against the illness and try to "work it off", with disastrous results. A public-health measure of real practical value is to educate not only medical practitioners but also the general public in these facts, though it is not easy to do this without accentuating the apprehension with which the appearance of poliomyelitis in epidemic form is viewed.

There have been many reports that bulbar poliomyelitis occurs with undue frequency in persons who have undergone tonsillectomy or adenoidectomy within the previous month[2,4,7,9,29,33,61] There have been a few reports denying the association, but the general opinion is that the risk is very real and that elective operations should not be performed when poliomyelitis is prevalent Some evidence has been produced that persons without tonsils, even though they may have been removed years beforehand, are more liable to bulbar poliomyelitis[65] The association of bulbar poliomyelitis with dental extractions has also been observed

Other forms of trauma such as blows and fractures have been associated with the appearance of paralysis in the injured limb A special form of trauma has recently been incriminated, namely, the effect of certain injections.[3,31,43] Since the publication of the original papers on this subject, a number of both contradictory and supporting reports have appeared. Space does not permit of a comprehensive review, but it may be said that there is now good evidence that in times of epidemic poliomyelitis intramuscular injection of the adsorbed combined diphtheria-pertussis prophylactic is followed within a month by paralysis in the injected limb more frequently than would be expected by chance Whether the same prophylactic injected subcutaneously has the same effect is uncertain, since this route is not often used because reactions tend to be more severe However, Rhodes[54] has found no evidence of an increased incidence of paralysis following the subcutaneous injection of a fluid (not adsorbed) combined diphtheria-pertussis prophylactic No convincing evidence incriminating other injections has been produced, with the notable exception of arsenicals, bismuth, and mercury[55] There is highly suggestive evidence that these heavy metals, injected intramuscularly, not only tend to precipitate paralysis in the injected limb, but actually increase the frequency with which paralysis develops This is a particularly important observation since hitherto it has been uncertain whether injections merely cause localization of a paralysis which would have occurred in any case, perhaps in another site, or whether they might precipitate paralysis in a case which would otherwise have been non-paralytic It is still not known whether the adsorbed diphtheria-pertussis prophylactic acts in the same way, but clearly this must now be considered a definite possibility

Fortunately the use of intramuscular injections of these heavy metals has decreased considerably since the advent of penicillin, and there is evidence that penicillin does not act in this way,[31] although this requires further investigation

However, the possibility of serious interference with dipththeria- and pertussis-immunization campaigns as a result of these observations rightly causes much anxiety Much capital has been made out of these incidents

by the opponents of vaccination procedures, and sensational reports have appeared in the press totally neglecting the great benefits of properly conducted immunization programmes, which vastly exceed any drawbacks, both in lives saved and in illness prevented. Nevertheless, this is small consolation to the parents of a healthy child who develops paralytic poliomyelitis after an injection. There are various ways of reducing this danger. The first is to avoid the use of the adsorbed combined prophylactic during times of prevalence of poliomyelitis. As recommended by the WHO Conference of Heads of Laboratories Producing Diphtheria and Pertussis Vaccines [67] and endorsed by the WHO Expert Committee on Poliomyelitis at its first session,[68] in times of severe epidemics it may be wise to suspend temporarily all immunizations in the locality affected. If the epidemic is of minor severity the use of the adsorbed combined prophylactic should be avoided, but immunization with the separate prophylactics may be continued. It would appear from the findings of Rhodes [51] that the use of fluid (not adsorbed) combined vaccine by the subcutaneous route is not accompanied by undue risk. Bousfield [11] advocates early immunization as a solution since the incidence of poliomyelitis in infants under six months is low. This might well be expected to reduce the risk during primary immunization; many authorities, however, consider that after early primary immunization an additional reinforcing dose is needed in the second year as well as the usual one at the age of school entry. Other precautions must be taken to reduce the risk at these times.

SPECIFIC PUBLIC-HEALTH MEASURES IN THE CONTROL OF POLIOMYELITIS

The above review of the epidemiology of poliomyelitis as it affects the application of public-health measures for the control of the disease gives the general background on which the measures to be adopted should be based. Clearly the actual measures to be applied in a given country will depend on the epidemiological circumstances in that country.

Public-health measures are particularly indicated in countries in which poliomyelitis occurs in the form of severe epidemics. Where the disease is still largely endemic, there is little need for extensive public-health measures, and, indeed, they would not be likely to have much effect. As to the specific measures which might be applied in the epidemic areas, it would appear that the first report of the WHO Expert Committee on Poliomyelitis contains as clear and concise a statement on the subject as can be made in the light of present knowledge. The relevant paragraphs of the report are therefore reproduced below.

Control Measures [f]

Introduction

From the time when poliomyelitis was first recognized to be an infectious disease until about 1930, various types of control measures were applied in an endeavour to check its spread However, none of the methods used appeared to be successful, and so in recent years the common attitude of health authorities has been that the general control measures usually applied to other infectious diseases are of little avail in poliomyelitis. This idea has received support from the pronouncements of certain authorities that, at the time of an epidemic, there are many hundreds of persons with inapparent infection for every case of paralysis Although this may be true in very extensive and severe epidemics, virological studies of certain communities have indicated that the virus has been found mainly in the intimate associates of the paralytic case For this reason, it appears possible that some reduction in the number of paralytic cases may be achieved by quarantine measures centred particularly around the first paralytic cases occurring in a community

Institution of control measures will probably have an even greater chance of reducing the number of paralytic cases in isolated rural or island communities. Here not only may measures be exerted against an individual infected household, but it should also be possible to prevent the entry into an apparently healthy community of individuals from infected localities

Many attempts have been made in the past to use convalescent serum as a prophylactic or therapeutic measure in poliomyelitis, without any conclusive evidence of its efficacy having been obtained. Improved methods of the fractionation of plasma have been introduced and it is apparent that antibodies against poliomyelitis, as well as against many other infections, are concentrated in the gamma-globulin fraction of pooled adult human plasma Experiments in monkeys and chimpanzees, and to a lesser extent in man, have shown that if this gamma-globulin is given before exposure paralysis may be prevented. Thus, this material, which is now in short supply, may be a useful measure of control under special circumstances. [g]

A more promising method of control is the possible use of prophylactic vaccines [h] which are not yet available However, the results of numerous experiments in primates and a growing experience from the experimental use of vaccine in man indicates the probability that a poliomyelitis vaccine may become available to the health officer in the not too distant future.

[f] With the exception of reference f footnotes in this section are the responsibility of the author and did not form part of the committee's report — ED

[g] See the article by Hammon (page 357)

[h] See the articles by Sabin and by Koprowski (pages 297 and 315)

The various methods of control of the disease will be discussed under separate headings

Measures to reduce the spread of infection

Notification of cases [1]

All available aids, both clinical and laboratory, should be used in an attempt to make a definite diagnosis Cases considered to be poliomyelitis should be notified as either non-paralytic or paralytic.[1] Although the diagnosis of non-paralytic poliomyelitis is less reliable than that of paralytic poliomyelitis, the figures so obtained, along with those of mortality-rates, permit of some estimate of the severity of an epidemic, of a comparison to be made with data from other epidemics, and of an evaluation of the validity of the reporting A patient is considered clinically to have poliomyelitis for purposes of notification if the symptoms and signs correspond with the following descriptions

(*a*) *Non-paralytic poliomyelitis*

An illness characterized by fever, headache, vomiting, sore throat, listlessness, stiffness of neck and back , pains in the back, neck, trunk, or limbs, and hyperaesthesia ; cerebrospinal fluid changes are usually found. The diagnosis is often strongly supported by epidemiological evidence , for example, known contact with a paralytic case or residence in an epidemic area

(*b*) *Spinal paralytic poliomyelitis*

Signs and symptoms of non-paralytic poliomyelitis with the addition of partial or complete paralysis of one or more muscle groups, detected on two examinations at least 24 hours apart.

(*c*) *Bulbar paralytic poliomyelitis*

Signs and symptoms of non-paralytic poliomyelitis with involvement of the cranial nerves and/or medullary centres

Isolation of the patient

It is established practice in some countries for patients to be isolated for 1-3 weeks from the onset of the major illness if paralytic, or from the onset of symptoms in non-paralytic cases Periods of isolation longer

than three weeks may be considered advisable under special circumstances, since excretion of virus in faeces may continue for several weeks.

When conditions permit, isolation of the patient in his home should be considered. If the patient is removed from his home, it should be to a hospital or unit for infectious diseases, a special hospital for poliomyelitis patients, or an isolation unit (one or more rooms) in a general hospital.

Suspected cases who are removed to hospital should preferably be isolated from known cases of poliomyelitis until the diagnosis is confirmed.

At some future date, it may be possible to determine the periods of isolation for individual patients by using tissue cultures as a means of detecting the presence of virus in the faeces.

Concurrent disinfection Throat discharges and faeces are infectious and should be disposed of as quickly and safely as possible Soiled articles should be promptly disinfected by heat Patients should have individual bed-pans unless immediate cleansing and sterilization by heat is possible

All those attending the patient should be instructed that the disease is highly infectious and that they must practise maximum hygienic precau- [illegible]

should not attend other patients while caring for acute poliomyelitis patients.

Terminal disinfection. A hospital isolation unit (or room), after being used for poliomyelitis patients, and before being opened to receive other cases, should be washed thoroughly with soap and water

Patients should not be moved to an orthopaedic ward or hospital until the locally approved period of isolation is complete Poliomyelitis convalescents may still be excreting virus in the stool, and therefore should not associate for 6-8 weeks from the onset of the disease with other orthopaedic patients or others in swimming-baths for rehabilitation or pleasure. If possible, poliomyelitis patients should have completely separate rehabilitation units.

Measures regarding contacts

The family Family and intimate associates, especially children, should be considered as probably infected Children with familial or intimate exposure should be confined to their homes for 21 days, avoiding overexertion Adults need not be confined, but should refrain from overexertion and should observe maximum hygienic precautions, they should refrain from association with children other than their own, and should avoid intimate contact with adults. They should not handle foodstuffs

served outside the family. Any associates who do not feel well should go to bed and a physician should be consulted.

Day-nurseries and nursery schools. Numerous investigations have demonstrated a very high infection-rate in infants associated with paralytic cases in such institutions If a case occurs, nursery schools should be closed and the staff, all the children, and their siblings should be treated in the same manner as family associates The parents of such children should observe maximum hygienic precautions and refrain from over-exertion.

Residential nurseries, schools, and children's camps If a case occurs in such a community, the other residents should be kept under observation for at least 21 days and instructed to avoid over-exertion , no new children or adults should be introduced. It should be remembered that if the residents are dispersed to their own homes they may seed the virus in a number of presumably unaffected communities.

Measures regarding the community

The public should be instructed in the probable modes of spread of the disease, and advised to take the following precautions in epidemic periods . [*]

1 Wash hands frequently, especially after defaecation and before eating.

2 Protect food from flies, and thoroughly wash uncooked food, such as fruit and vegetables

3. Avoid intimate associations (shaking hands, common eating utensils, communal towels, etc) with members of a family in which a case of poliomyelitis has occurred within three weeks

4 Treat all febrile illnesses with caution , bed rest or at least the avoidance of over-exertion for a period of a week is advisable

5. Avoid over-exertion, particularly if not feeling perfectly well

6 Unnecessary travel into or out of communities where the disease is prevalent should be discouraged

7 In the presence of a severe local epidemic it would be wise to delay opening schools after the summer holidays, but normally schools need not be closed nor public gatherings forbidden Swimming-pools with adequately chlorinated water need not be closed, but should not be overcrowded. Unchlorinated pools should be closed.

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[*] It should be remembered that in some countries the appearance of epidemic polio-

If, in the future, isolation and quarantine applied on a national level should prove to be of real value as methods of prevention of epidemics, some countries, particularly those where the general level of immunity in the population is low, might be inclined to apply quarantine on an international level as well The committee feels that, at present, restrictions of international travel would not be justified and recommends that the developments in this field be closely followed by the proper authorities.

Measures to reduce the incidence of paralysis

It has already been mentioned that a number of factors may predispose to or precipitate paralysis Some reduction in the incidence of paralysis may be expected to result from attention to the following principles

1 Elective operations for the removal of tonsils and adenoids should not be carried out during epidemic prevalence of poliomyelitis

2 The activity of persons suffering from an illness in which there is reason to suspect poliomyelitis should be restricted for a week, preferably by rest in bed

3. Persons in intimate association with a case of poliomyelitis should take the minimum amount of exercise during the period in which symptoms might be expected to develop, that is, between 5 and 21 days after exposure Fatigue from any cause, including travel, should be avoided

4. With regard to immunizations and injections, of which mention has [already] been made, the following extract from the report of the WHO Conference of Heads of Laboratories Producing Diphtheria and Pertussis Vaccines[67] is endorsed by the committee

'The conference feels that the effectiveness of diphtheria- and whooping-cough-immunization campaigns should be disturbed as little as possible by the fear of subsequent poliomyelitis Immunization against diphtheria and whooping cough should normally be continued during the poliomyelitis season, but if the disease should assume serious epidemic proportions in any given area, all immunization should be temporarily suspended in that locality If, in the opinion of the local health authority, the epidemic is of minor severity, then immunization with diphtheria and whooping-cough vaccines may be continued, but the use of adsorbed combined vaccine should be discouraged '

5 It seems advisable to suspend during epidemics of poliomyelitis the large-scale use of intramuscular injections of an irritant character, for example, organic arsenicals and heavy metals

6. In view of the possibility that the skin may be contaminated with poliomyelitis virus, before administering an injection, cleansing with tincture of iodine is recommended, and separate heat-sterilized syringes and needles should be used for each patient [1]

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[1] Alternatively, if individual syringes cannot be used devices designed to prevent contamination of the nozzle of the syringe may be considered, e g, that devised by Professor R Gispen (see *Lancet* 1952, 2 171)

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